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Synthesis of biologically active indole-fused heterocyclic derivatives

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University of Wollongong

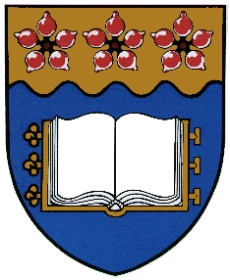
SYNTHESIS OF BIOLOGICALLY ACTIVE INDOLE-FUSED HETEROCYCLIC DERIVATIVES

A thesis submitted in fulfillment of the requirements of the award of the degree

DOCTOR OF PHILOSOPHY

from

UNIVERSITY OF WOLLONGONG



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CERTIFICATION

I, Waya Sengpracha, declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Waya Sengpracha

10 February 2005

PUBLICATIONS

1. A free radical cyclisation approach to indolo-benzodiazocine derivatives (Bremner, J.; Sengpracha, W. *Tetrahedron*, **2005**, *61*, 941-953)

2. An iodoacetamide-based free radical cyclisation approach to the 7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5H)-one (Paullone) system (Tetrahedron, submitted)

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LIST OF ABBREVIATIONS

Abs ETOH	absolute ethanol
Ac	acetyl group
AIBN	α,α′-azobis(isobutyronitrile)
Ar	aryl group
$CHCl_3$	chloroform
CI-MS	chemical ionization mass spectrometry
^{13}C NMR	carbon 13 nuclear magnetic resonance spectroscopy
conc.	concentrated
d	doublet (NMR spectroscopy)
dd	doublet of doublets (NMR spectroscopy)
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer (NMR spectroscopy)
DMAP	4-(dimethylamino)pyridine
DME	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EC_{50}	excitatory concentration
EI-MS	electron impact mass spectroscopy
EtOH	ethanol
EtOAc	ethyl acetate

equiv.	equivalent
g	gram
gCOSY	gradient correlated spectroscopy
gHMBC	gradient heteronuclear
gHSQC	gradient heteronuclear single quantum coherence spectroscopy
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HR-MS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	inhibitory concentration
J	coupling constant (NMR spectroscopy)
K_2CO_3	potassium carbonate
kg	kilogram
LAH	lithium aluminum hydride
LR-MS	low resolution mass spectrometry
M	molar
Me	methyl group
mg	milligram
µL	microlitre
mL	millilitre
min	minute
m/z	mass to charge ratio (mass spectrometry)
NaI	sodium iodide
NOESY	nuclear overhauser and exchange spectroscopy

PTLC	preparative thin layer chromatography
pet. spirit	petroleum spirit
R_f	retention factor (TLC)
r.t.	room temperature
s	singlet (NMR spectroscopy)
satd.	saturated
t	triplet (NMR spectroscopy)
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

ABSTRACT

New synthetic routes to 1,2- and 2,3-fused indoles with seven- or eight-membered rings have been developed in this project, with the longer term aim of assessing their biological activity. Approaches to such fused indole derivatives were accessed via free radical cyclisation from 1- or 2-substituted indole derivatives with haloacetamide precursors. Using 1-substituted indole derivatives with haloacetamide functionalites, free radical cyclisation reactions gave fair yields of the indole- and dihydroindole-fused eight membered ring derivatives. Using 2-substituted indole derivatives with haloacetamide functionalities, prepared in turn by a palladium-mediated cyclisation of *N*-substituted indoles followed by hydrolysis and subsequent decarboxylation, free radical cyclisation afforded the 7,12-dihydro-indolo[3,2-*d*]benzazepin-6(5*H*)-one (Paullone) system in fair yields.

A novel synthetic approach to a bis-indole fused seven-membered ring system was developed based on an *N*-substituted spirooxindole rearrangement. The spiro-indolinols obtained from partial amide reduction underwent rearrangement to give the bis-indole fused seven-membered ring derivatives **270** and **271** under acidic conditions.

Antimicrobial activity of the indole fused eight-membered ring systems was evaluated. The compound 5,14-dihydro-10-methoxy-5-methoxy-5-methyindolo[2,1-*d*][1,5]benzodiazocin-6-one **186c** showed by far the most potent antibacterial activity (against *Staphylococcus aureus*), while 5,14-dihydro-5-(4-methoxybenzyl)indolo[2,1-*d*][1,5]benzodiazocine-6-one **186d** showed good *in vitro* antimalarial activity against both drug resistant and drug sensitive strains of *Plasmodium falciparum*. These two compounds represent novel structural leads for such activities.

ACKNOWLEDGEMENTS

I would like to thank all those who have helped me throughout my study, especially thanks to my supervisor, Prof. John B. Bremner for his guidance and support during the course of this study. Thank you to the Royal Thai Government for the provision for my scholarship.

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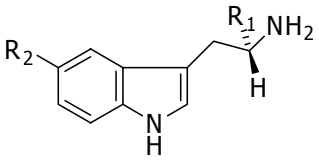
Lastly, thanks to my family for their unconditional love and support.

1 Introduction

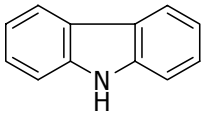
1.1 Introduction to indoles

Indole derivatives have been a topic of substantial research interest and continue to be one of the most active areas of heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities.[1] A large number of indole derivatives are at the fore as pharmacologically active lead compounds for drug development. Indole derivatives also occur widely in many natural products such as those from plants,[2] fungi[3] and marine organisms.[4] The isolation, biological evaluation and chemical properties of natural products have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacists. Chemical and biological research has also presented a great challenge to synthesise and optimise highly efficient and economical synthetic routes to novel biologically active substances.

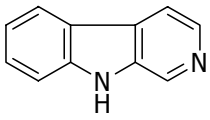
At present, there are approximately 1500 indole alkaloids described,[5] which includes simple and more complexly functionalised indole derivatives. The simple indole derivatives are comprised of a pyrrole ring fused with a benzene ring such as in the essential amino acid, tryptophan **1** as well as tryptamine **2** and serotonin **3**. More complex indole derivatives usually contain an additional fused ring, and in most cases a six membered ring such as in carbazole **4** and β-carboline **5**.



1 $R_1 = CO_2H$, $R_2 = H$
2 $R_1 = R_2 = H$
3 $R_1 = H$, $R_2 = OH$



4 Carbazole



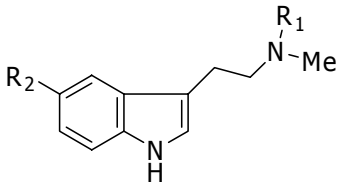
5 β–Carboline

1.1.1 Bioactive indoles

There are several thousand indole derivatives known and many of these have important pharmacological activity. Some natural product based bioactive indoles are discussed here and are classified in terms of the number of indole rings present and the presence or absence of indole ring fusions.

1.1.1.1 Mono indoles

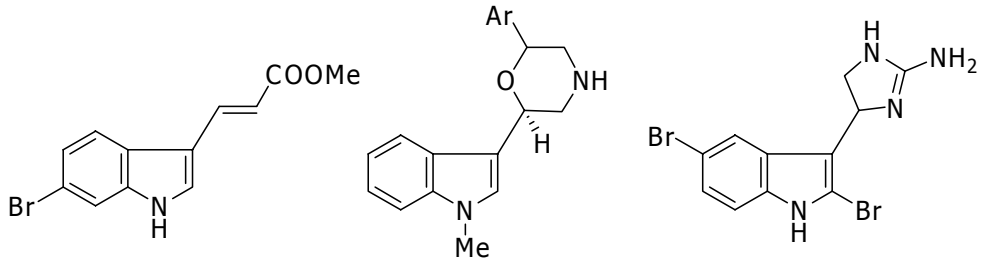
The medicinal uses of the simple tryptamine alkaloids are relatively few. Serotonin **3** is one of the key neurotransmitters in animals. Many indole derivatives found in plants have been noted to have hallucinogenic activity in humans, for example bufotenine **6**, and 5-methoxy-*N*-methyltryptamine.



6 $R_1 = Me$, $R_2 = OH$
7 $R_1 = H$, $R_2 = OMe$

Some simple indole alkaloid derivatives have also been isolated from marine sources. For example, methyl-(*E*)-3-(6-bromo-3-indolyl)-3-propenoate **8**, a known sponge metabolite has been isolated from a number of sponges.[6-8] Further examples of simple bioactive indole alkaloids from marine natural products are compounds **9** and **10**. The

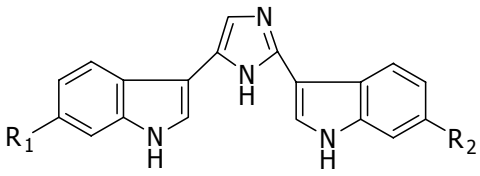
alkaloid (±)-chelonin A **9**, isolated from a marine sponge of the *Chenolaplysilla* sp.,[9] showed potent antimicrobial and anti-inflammatory activities. Discodermindol **10**, was discovered in *Discodermia polydiscus* and showed moderate cytotoxic activity.[10]



8 **9** **10**

1.1.1.2 Bis-indoles

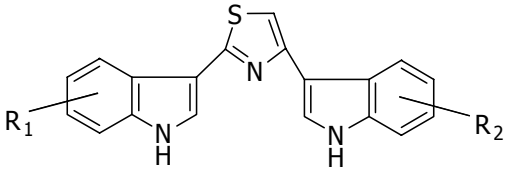
Bis-indole alkaloids are an important structural class due to their high degree of biological activity. For example, the nortopsentins A-C[11] **11a-c**, exhibit *in vitro* cytotoxicity against P388 cells with IC_{50} (inhibitory concentration) values of 7.6, 7.8, and 1.7 μg/mL, respectively. These alkaloids were isolated from the deep water marine sponge *Spongsorities ruetzleri*. On the basis of these lead compounds, the imidazole moieties of nortopsentins were replaced with a thiazole, pyrazinone or pyazine ring.[12,13]



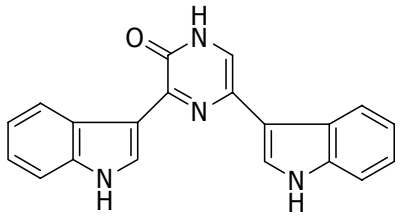
Nortopsentin A **11a** $R_1 = R_2 = Br$
Nortopsentin B **11b** $R_1 = Br$, $R_2 = H$
Notopsentin C **11c** $R_1 = H$, $R_2 = Br$

The 2,4-bis(3´-indolyl)thiazoles **12** exhibited selective cytotoxicity against certain leukemia cell lines with GI_{50} (growth inhibition) values in the low micromolar range. The

2,4-bis(3′-indolyl)pyranzinone **13** and the 2,4-bis(3′-indolyl)pyrazine **14** also displayed a broad spectrum of cytotoxic activity, particularly compound **14**, which possessed very strong inhibitory activity against all cell lines with GI_{50} values in some cases less than 10 μM.



12 R_1, R_2 = Br, OMe



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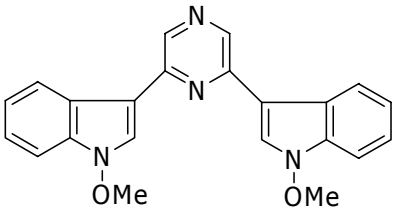

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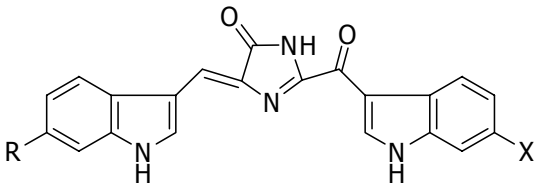
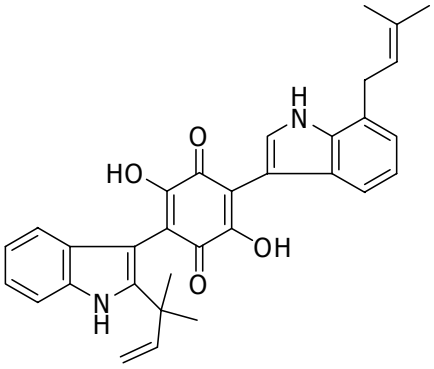


Rhopaladin B **15a** R = OH, X = H
Rhopaladin C **15b** R = H, X = Br

Isolation of compounds from extracts of the Okinawan tunicate, *Phopalawa* spp., afforded four bis-indole alkaloids,[14] of which two possessed very interesting biological activity. Rhopaladin B **15a** exhibited inhibitory activity against cyclin dependent kinase 4 and *c-erbB*-2 kinase (IC_{50} values of 12.5 and 7.4 μg/mL, respectively) and rhopaladin C **15b** showed antibacterial activity against *Sacina lutea* and *Corynebacterium xerosis* (MIC; minimum inhibitory concentration; 16 μg/mL). Structural variety in the bis-indole series is further exemplified by the fungal metabolite, demethylasterriquinone B1 **16**, which is a selective activator for the insulin receptor.[15]



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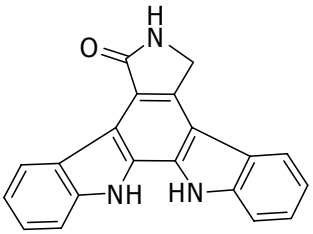
1.1.1.3 Annelated indoles

Increased structural complexity in indole-based products is seen with fusion of the indolic moiety to other rings. For example a number of dimeric indole alkaloids with a fused six-, seven-, or eight-membered ring between the two indole rings are known with many of them also being biologically active. For instance, the indolo[3,2-*a*]carbazole[16] **17**, with a bis-annelated six-membered ring, displayed antitumour properties and, in particular, inhibition of protein kinase C, while the slime mold alkaloid arcyriacyanin A[17] (**18**), with a seven-membered ring, is known to inhibit protein kinase C and protein tyrosine kinase. As a result, **18** exhibited a unique inhibitory profile against a panel of human cancer cell lines.



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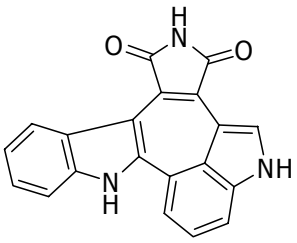

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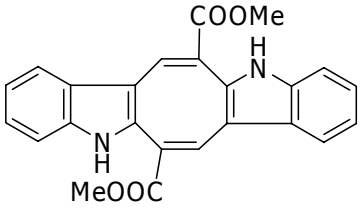
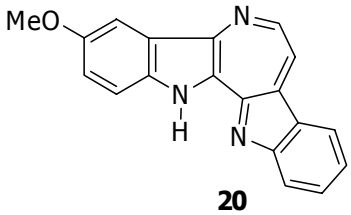


19

The bis-indole fused derivative with an eight membered ring, the caulerpin **19**, was isolated from the green alga *Caulerpa racemosa*. This alkaloid showed weak *in vitro* antitumour activity[18] together with plant growth regulatory activity.[19] The structural motif

of two indoles fused to a seven-membered ring occurs in the novel iheyamine pigments **20** and **21**,[20] which were isolated from a colonial ascidian *Polycitorella* sp.. Both compounds exhibited moderate cytotoxicity.



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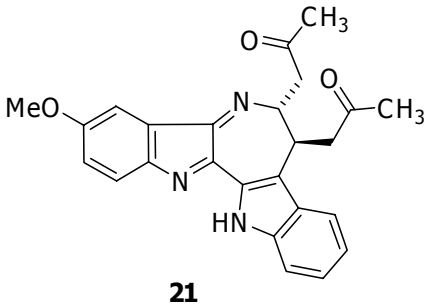
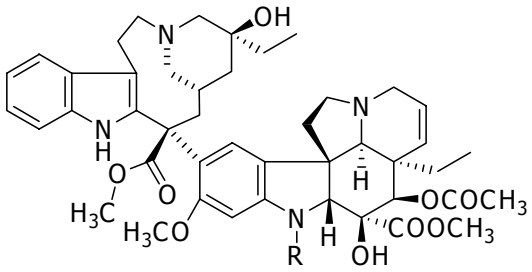
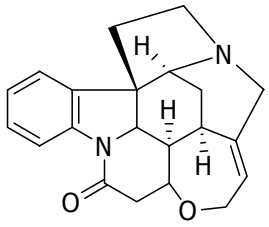


21

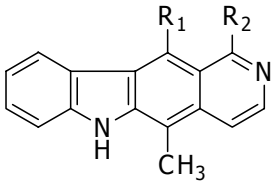
Related to the annelated bis-indole derivatives are a number of other derivatives which possess one annelated indole or modified indole skeleton. Valuable members of this group are vinblastine **22a** and its analogue vincristine **22b**, which are alkaloids isolated from *Catharanthus roseus* (Apocynaceae). These two alkaloids are currently used clinically[2] to treat Hodgkin's disease and other lymphomas, testicular cancer, and a variety of solid neoplasms. They are also used to treat patients with neuroblastoma, choriocarcinoma, and Kaposi's sarcoma.



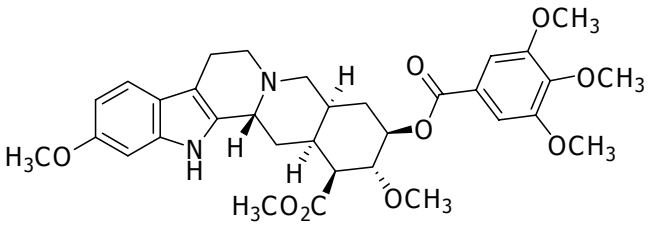
22a Vinblastine, R = CH_3
22b Vincristine, R = CHO



23 Strychnine



24a Ellipticine, $R_1 = CH_3$, $R_2 = H$
24b Olivacine, $R_1 = H$, $R_2 = CH_3$



25 Reserpine

Other examples of bioactive alkaloids with one fused indolic moiety include strychnine, ellipticine, olivacine and reserpine. Strychnine **23** was once used to control rodents, but it has been replaced by poisons which are less toxic to man. Currently, strychnine is used in patients with eye disorders and optic nerve atrophy.[2] Ellipticine **24a** and olivacine **24b**, which contain a pyrido[4,3-*b*]carbazole nucleus,[21] have remarkable antitumour activity but unfortunately have not progressed to clinical use. Reserpine **25**[2] was a key drug in the treatment of hypertensive, nervous and mental disorders.

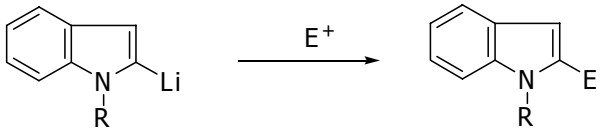
1.2 Indole synthesis

Most generally applicable synthetic methods for the indole moiety involve ring closure to form the pyrrole ring of indole. Substituents are often introduced prior to the synthesis of the ring system. The classical Fischer method has maintained its prominent role as the most common synthetic route to indole derivatives for more than a century.

Other cyclisation reactions have been reported including the Bischler synthesis, palladium-catalysed cyclisation, photocyclisation and radical cyclisation. These and other indole cyclisation reactions have been reviewed elsewhere.[1,22,23]

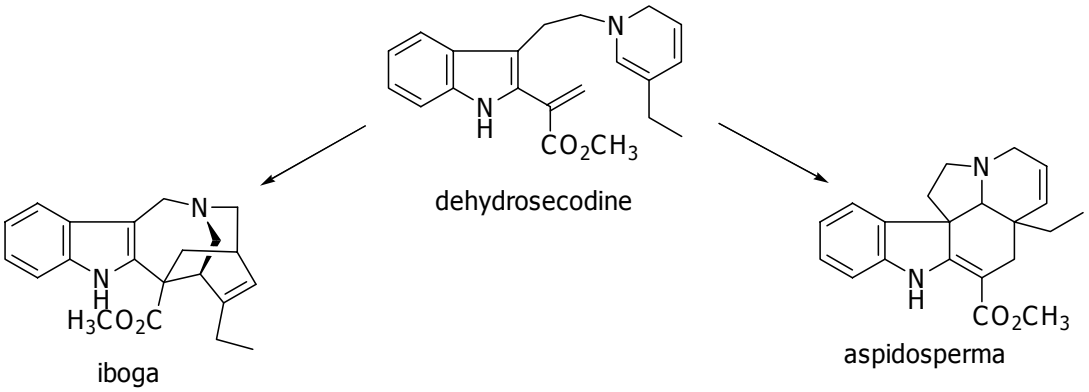
An example of Fischer indolisation is in the synthesis of the marine alkaloid eudistomidin-A[24] and other fused indoles which have been synthesised using the Fischer indole strategy.[25]

Indole derivatives can also be accessed by further functionalisation of the indole nucleus. For example, the indolic NH which is weakly acidic, upon treatment with a strong base, can form the indolide anion which is capable of subsequent reaction with electrophiles at either the nitrogen atom or at the 3-position of the indole.[26] Nitrogen substitution is favoured by the use of more ionic sodium and potassium salts with strong electrophiles and also by the use of dipolar aprotic solvents. This type of *N*-substitution is important for the introduction of protecting groups.[27] Lithiation of *N*-substituted indoles is selective for C-2 because of the influence of the heteroatom,[1] and therefore this is useful for preparing C-2 substituted indoles by reaction with electrophiles (Scheme 1-1).



Scheme 1-1. Lithiation of *N*-substituted indoles.

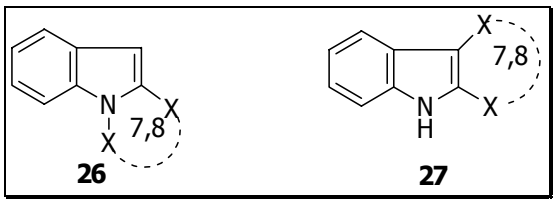
Indolic derivatives can also be elaborated upon using cycloaddition reactions to construct indole fused rings. For example, cycloaddition using Diels-Alder reactions of 2- and 3-vinylindoles with dienophlies results in partially hydrogenated carbazoles.[1] 2-Vinylindole derivatives have also been used in the synthesis of both aspidosperma and iboga alkaloids[28] (Scheme 1-2) from dehydrosecodine.



Scheme 1-2. Example of Diels- Alder reaction of 2-vinylindole.

1.3 Indole fused seven- or eight-membered ring systems

As a result of the chemical and pharmacological importance of indole derivatives, a wide range of indoles and derivatives including fused- and non fused-indoles have been prepared. However, only a limited number of indole fused seven- or eight membered rings have been reported. In order to assess this more accurately and to provide a contextual framework for the work described in this thesis, a survey was undertaken of the relevant literature (SciFinder Scholar) restricted mainly to indole fused seven- or eight-membered ring compounds with one, two, and three nitrogens in the medium sized ring and based on the 1,2-fused systems **26** and the 3,4-fused systems **27**. The results are discussed in the following Sections 1.3.1 and 1.3.2.



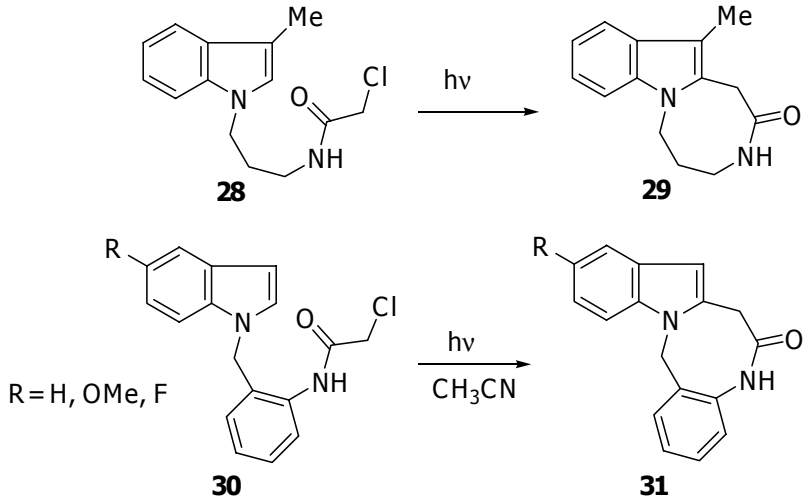
1.3.1 Synthesis of indole-1,2-fused seven or eight membered ring systems

A variety of synthetic methodologies for 1,2-fused indole systems have been developed. These include intramolecular C-C bond formation, eletrophilic cyclisations,

additions to carbonyl groups, radical cyclisations and coupling reactions. The direct ring expansion of a smaller ring to a seven- or eight-membered ring has also been used to synthesise such fused indole derivatives. The methodologies used to form indole-fused seven- and eight-membered rings at the 1,2 position are classified according to the substrates utilised and the bond formed in the ring-closing step.

1.3.1.1 Bond formation to C-2; ring closure via *N*-substituted indoles

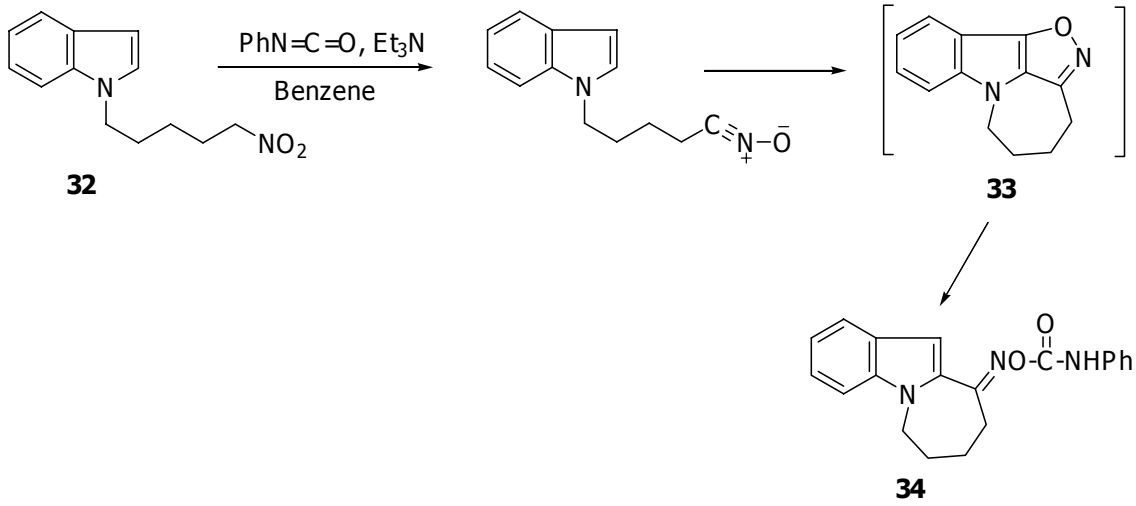
Indolo[2,1-*d*][1,5]diazocinone derivatives[29,30] **29** and **31** have been synthesised by photocyclisation of the chloroacetamides **28** and **30**, respectively (Scheme 1-3). However, a number of by-products were produced and low yields of the desired products were obtained.



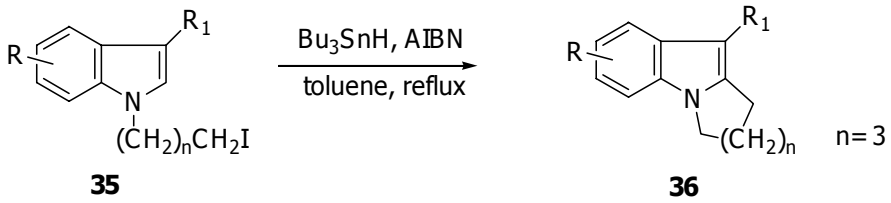
Scheme 1-3. Photochemical cyclisation of chloroacetamides.

Intramolecular nitrile oxide-olefin cycloaddition of an *N*-substituted indole **32**[31] in the presence of phenyl isocyanate at 20 ^{o}C, via **33**, led to a fused 7-membered ring derivative **34** in 20% yield (Scheme 1-4). This ring fusion involved the heterocyclic double bond in the cycloaddition.

Radical cyclisation of the 1-(ω-iodoalkyl)indole-3-carbaldehydes **35** with tributyltin hydride and AIBN resulted in the formation of the 1,2-fused indole **36** (Scheme 1-5).[32,33] However, the 7-membered ring analogue was obtained in significantly lower yield than the corresponding 5- and 6-membered ring analogues.[33]

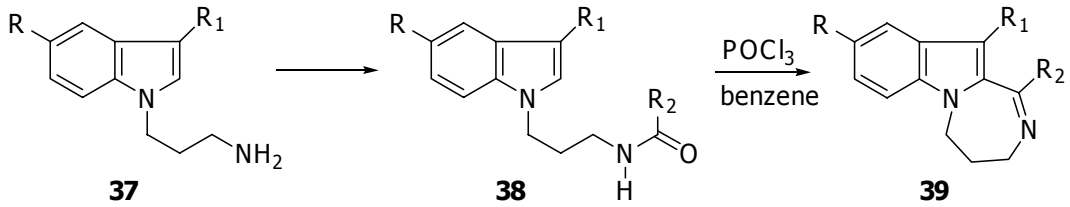


Scheme 1-4. Intramolecular nitrile oxide-olefin cycloaddition.



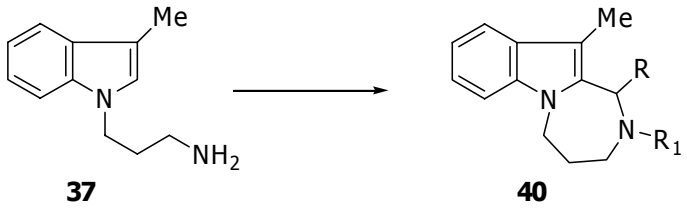
Scheme 1-5. Radical cyclisation of alkylhalides.

Cyclodehydration via a Bischler Napieralski type reaction of acetyl and benzoyl derivatives **38** (R= H, Me, OMe, OEt, R_1= Me, Ph, R_2= Me, Ph), prepared from acylation of 3-aminopropyl derivatives **37**, resulted in indolo-diazepine derivatives **39** (Scheme 1-6).[34] Compounds **37** and **39** were tested for antiserotonin activity, with **39** (R= H, R_1= Ph, R_2= Me) showing high activity and **37** (R= R_1= Me) moderate activity.



Scheme 1-6. Cyclodehydration via a Bischler Napieralski type reaction.

The 1,4-diazepino[1,2-*a*]indoles **40**,[35] which are closely related in structure to the compounds **39**, have been synthesised by the Mannich condensation of the amine **37** with acetaldehyde or benzaldehyde. The resulting Mannich bases underwent intramolecular cyclisation to give the fused seven-membered ring derivatives **40** (R_1= H, R= CH_2-1-benzotriazole).

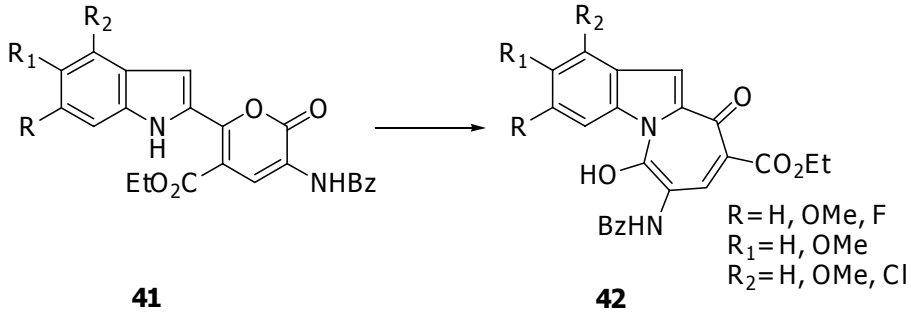


Also, the condensation of **37** (R= H, R_1= Me) with (1-hydroxymethyl)benzotriazole gave 1,4-diazepino[1,2-*a*]indole **40** (R= H, R_1= CH_2-1-benzotriazole) in 51% yield.[36] Elimination of the benzotriazole group can then give compounds of type **40** in good yield.

1.3.1.2 Bond formation to N-1; ring closure via 2-substituted indoles

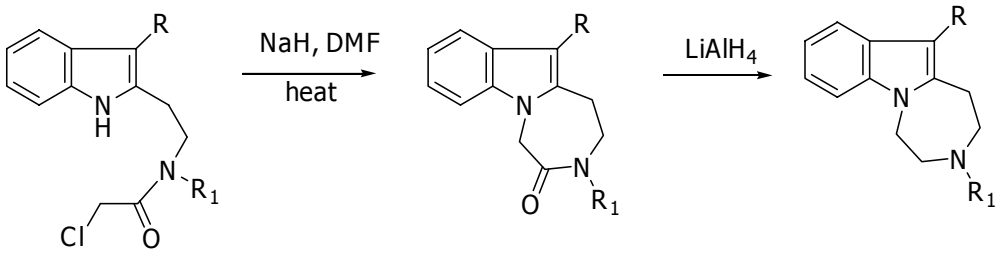
Gelmi *et al.*[37] reported the intramolecular condensation of 3-benzoylamino-6-(indol-2-yl)-pyran-2-ones **41** upon treatment with K_2CO_3 in refluxing acetonitrile to afford the corresponding azepino[1,2-*a*]indol-6-ones **42**. The mechanism involved the deprotonation of the benzoylamino group which subsequently rearranged to the indolide anion. The

intramolecular condensation of the indolide anion, with the near by electrophilic pyran-2-one moiety, gave compounds **42** in 50-80% yields.



41 **42**

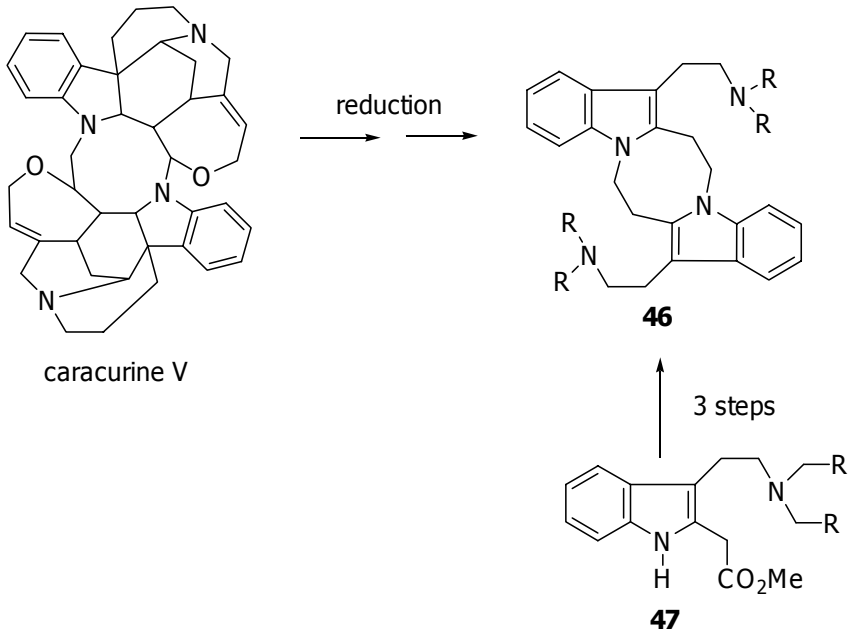
A patent by Gadient[38] described the synthesis of a variety of diazepinoindoles and their pharmaceutical use. 2,3,4,5-Tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole **45** (R= Ph, R_1= Me) and its derivatives were synthesised from **43** via indolide anion formation prior to ring closure. The compounds of type **45** are effective psychotropics, especially antipressants, by standard *in vivo* and *in vitro* tests;[38] other authors also reported useful CNS activity with these compounds.[39]



43 **44** **45**

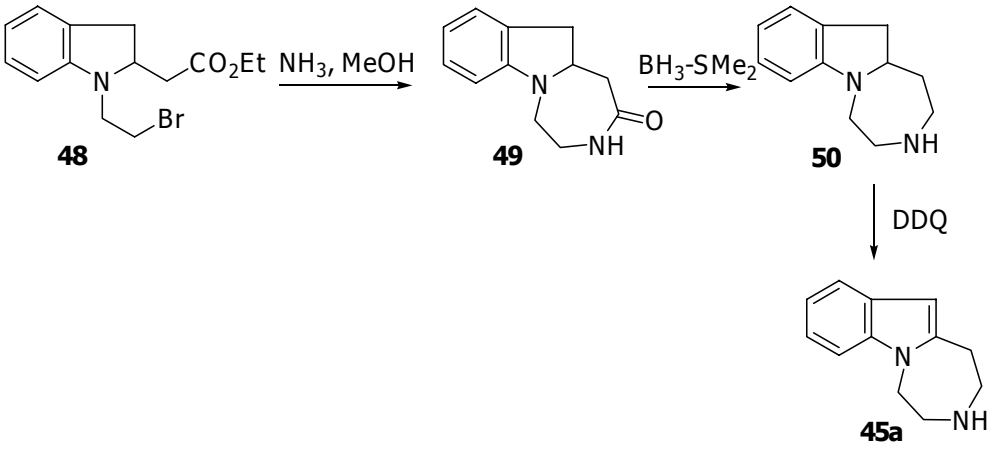
The *Strychnos* alkaloid analogues of caracurine V are among the most potent known allosteric modulators of the muscarinic M_2 receptor.[40] Reduction of the caracurine V skeleton gave the bioactive pentacyclic derivative **46** (R= CH_3). This novel ring system could become a new lead structure in the search for active muscarinic compounds.[41] The synthesis of the new bis-indole fused skeleton was also achieved starting from the known [3-(2-dibenzylaminoethyl)indol-2-yl]acetic acid methyl ester **47** (R= CH_2Ph).[42] The

compound **46** (R= CH_2Ph) was then obtained in 3 steps by employing a double alkylation strategy.[41]

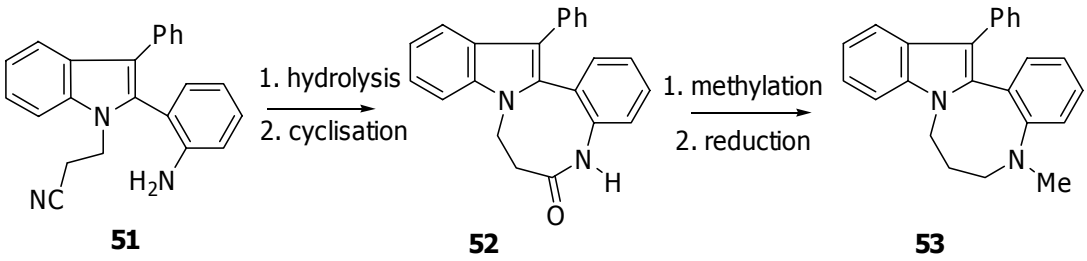


1.3.1.3 Medium ring formation via 1,2-disubstituted indoles

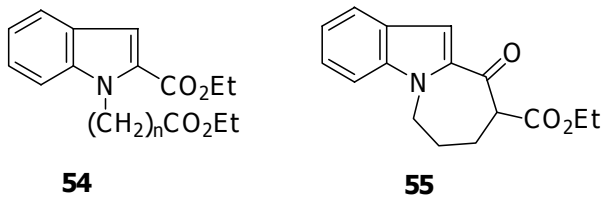
The synthesis of 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indoles **45** have been discussed previously based on 2-substituted indoles, but an alternative route to a specific derivative **45a** was reported from the *N*-substituted dihydroindol-2-yl acetate **48**. Treatment of **48** with ammonia-saturated methanol at 50 ^{o}C generated the lactam **49**. Reduction of **49** with borane-dimethylsulfide to **50** and subsequent oxidation with DDQ then generated 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole **45a**.[43]



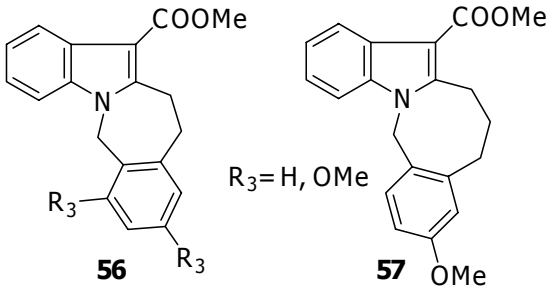
A cyclisation route to the indolo-1,5-benzodiazocine **53** has also been reported, starting from the 1,2-disubstituted indole **51**.[44] Hydrolysis of **51** gave the corresponding acid, which was then cyclised to **52**. *N*-Methylation of **52** followed by reduction by $LiAlH_4$ gave **53** which showed potential activity in the CNS.



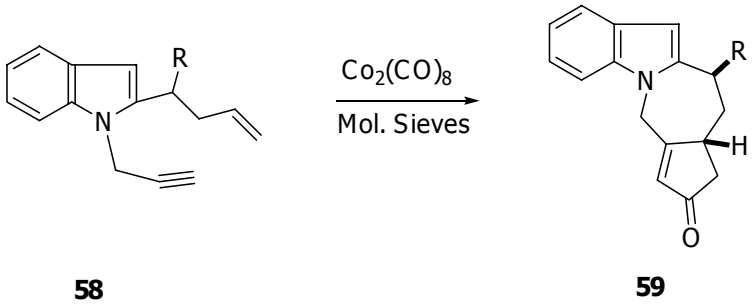
In a report from Bit *et al*., [45] the synthesis of the tetrahydroazepino[1,2-*a*]indole **55** was described based on a Dieckmann/ring expansion reaction after treatment of the indole **54** with potassium *tert*-butoxide (Me_3COK). This approach was claimed to allow the synthesis of a large variety of substituted systems required for the preparation of a series of potent and selective inhibitors of protein kinase C.



The cyclisation of *N*-Mannich bases of 2-substituted indoles[46] also gave the indolobenzazepines **56** and indolobenzazocine **57** in good yields.



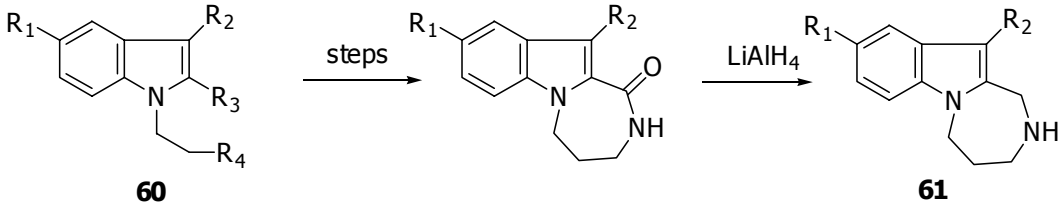
Seven membered ring formation via intramolecular Pauson-Khand reactions gave good yields of the enynoindoles **58**[47] via carbon-carbon bond formation (Scheme 1-7). The addition of molecular sieves to the reaction medium promoted the cyclisation product, probably due to the adsorption of the enyne and stabilisation of a pretransition state; ligand exchange may also be promoted.[48]



Scheme 1-7. Cyclisation via intramolecular Pauson-Khand reactions.

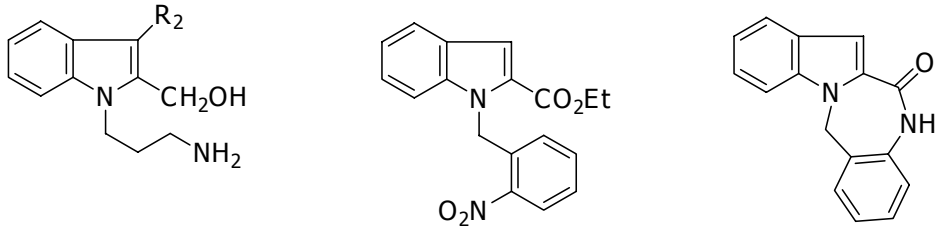
The 5-hydroxytryptamine antagonists **61** were prepared by intramolecular cyclisation of 1,2-disubstituted indoles **60** (R_3= CO_2Et, R_4= CN). Catalytic hydrogenation of **60** (R_3= CO_2Et, R_4= CN) using Raney-nickel gave **60** (R_3= CO_2Et, R_4= CH_2NH_2). Ring closure using sodium hydride in xylene followed by reduction with $LiAlH_4$ then gave the 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indoles **61** in good yields (Scheme 1-8).[49,50] Reduction of **60** (R_3= CO_2Et, R_4= CN) with $LiAlH_4$ gave **62**, however, attempted

cyclodehydration of **62** was unsuccessful. The biological testing for 5-HT antagonistic activity revealed that the potency of most of these compounds was less than that of cyproheptadiene, a standard anti-5-HT drug.[50]



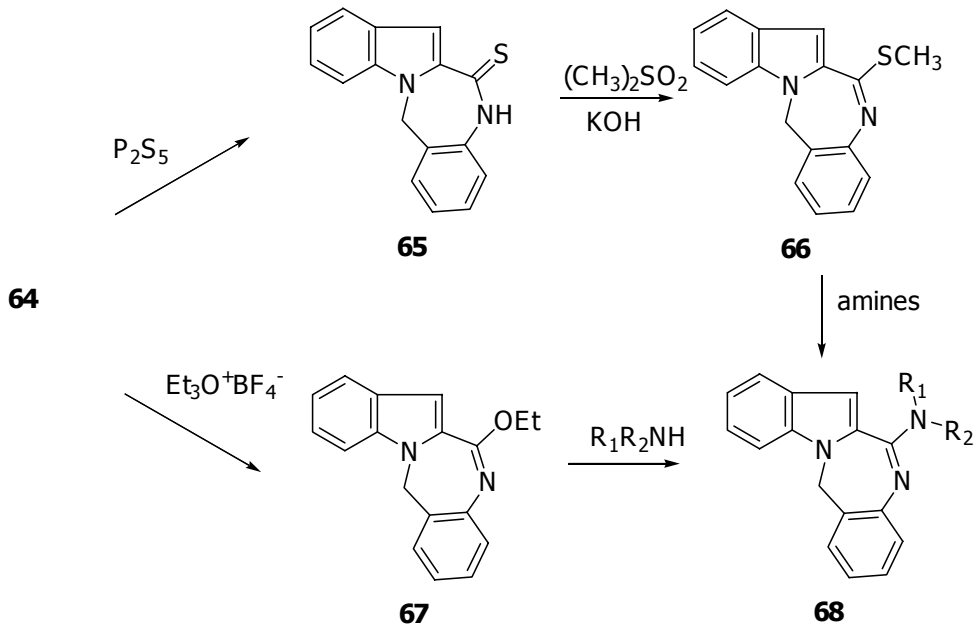
60 **61**

Scheme 1-8. Preparation of 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indoles.



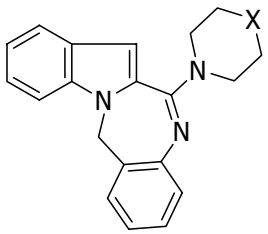
62 **63** **64**

A similar method to that described in Scheme 1-8 was employed to prepare the indolo[2,1-*c*][1,4]benzodiazepinone **64** from the alkylated nitro compound **63** followed by hydrogenation and thermal cyclisation. The alkylamino derivatives **68** were prepared from the lactam **64** via two methods (Scheme 1-9).[51] The first method involved the conversion of **64** to the thiolactam **65** by reaction with phosphorus pentasulfide, followed by alkylation with dimethyl sulfate. The resulting methyl thioester **66** was then reacted with various amines to give the amidines **68**. The other method involved the reaction of lactam **64** with triethyloxonium tetrafluoroborate to give the imino ester **67**, which was then reacted with amines in the presence of a catalytic amount of glacial acetic acid to give the amidines **68**.



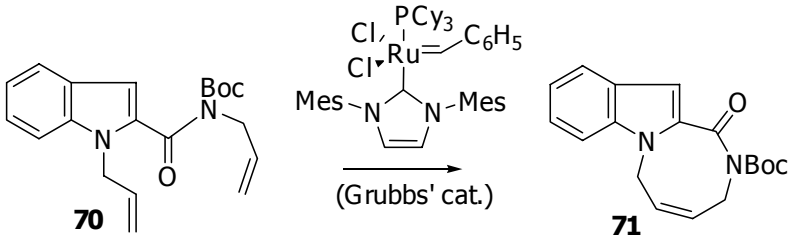
Scheme 1-9. Preparation of indolo[2,1-*c*][1,4]benzodiazepine derivatives.

A biological study of the cyclic alkylamino derivatives **69** showed that they possessed antithistamine and antiserotonin activities as well as the ability to inhibit mediator release. These agents thus have potential for the treatment of a variety of allergic conditions.



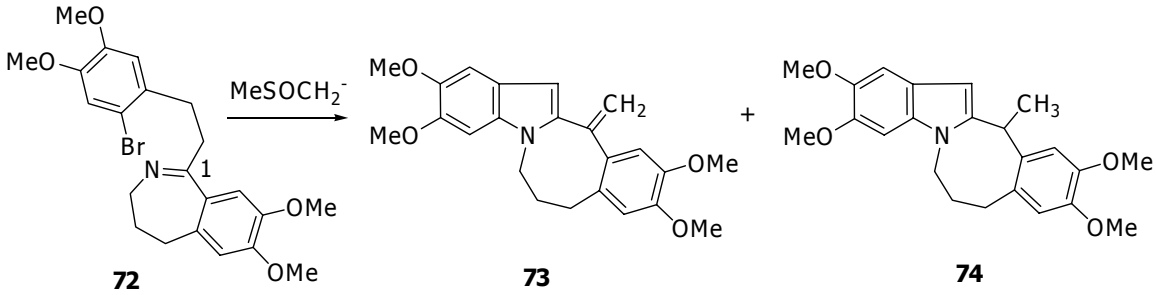
69

The indole fused eight-membered ring **71** was synthesised via the ring-closing methathesis of *N*-allyl-1-allyl-1*H*-indole-2-carboxamide derivative **70**.[52] Ring closure utilising Grubbs' catalyst afforded the eight membered ring, although only in low yield (13%).



1.3.1.4 Indole ring formation

A quite different alternative approach to indole fused ring systems is via formation of the indole ring itself. This is illustrated by the synthesis of the indolo[1,2-*a*][3]benzazocines[53] **73** and **74** in 43 and 8% yields**,** respectively**,** by treatment of the benzazepine **72** with dimsylsodium in DMSO. The mechanism involves the attack by the $MeSOCH_2$ anion at C-1, followed by a ring closure-ring cleavage process.

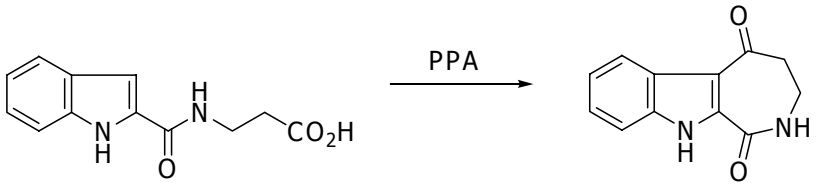


1.3.2 Synthesis of indole-2,3-fused seven or eight membered ring systems

Construction of indole fused rings at the 2,3-position may involve the use of indole substitution at either the 2- or 3-position, or at both the 2- and 3-positions followed by cyclisaton reactions or substitution reactions and then cyclisations. The following examples of indole 2,3-fused ring systems are classified according to the substitutent position on the indole ring starting materials.

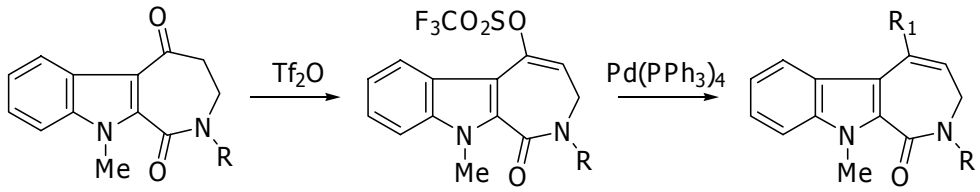
1.3.2.1 Ring closure at C-3 via 2-substituted indoles

Suzuki *et al*.[54] reported the cyclisation at C-3 of *N*-(2-indolecarbonyl)-β-alanine **75** with polyphosphoric acid (PPA) to give the fused seven-membered ring derivative **76** as the major product.



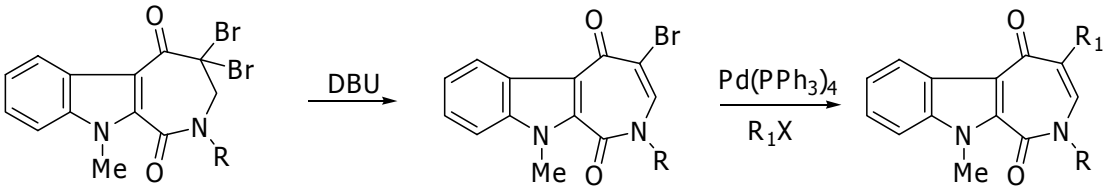
75 **76**

A set of related 5-substituted azepinoindoles **78** have been prepared starting from compounnd **77**, a derivative of **76**, via reaction with trifluoromethanesulfonic anhydride followed by functionalisation at the 5-position via palladium catalysed reactions with commercially available stannanes. Compound **78**, with R= H and R_1= 2-thienyl, was evaluated for growth inhibitory activity against murine leukemia L1210 cell lines;[55] weak *in vitro* cytotoxicity was observed (IC_{50}> 10 μM).



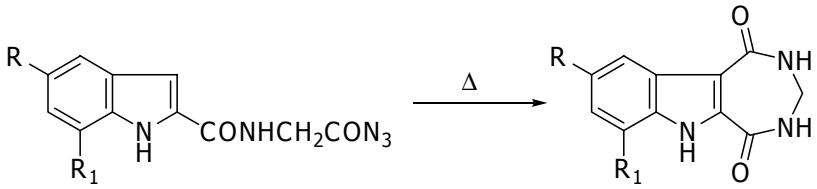
77 **78**

Reactivity studies on **76** revealed that electrophilic attack at the α-position to the ketone in the azepino ring was feasible,[55] and in this way the dibromo derivative **79** was achieved by direct bromination of **76**. Elimination of HBr followed by palladium-mediated cross-coupling reactions then gave the 4-substituted azepinones **80**.[56]



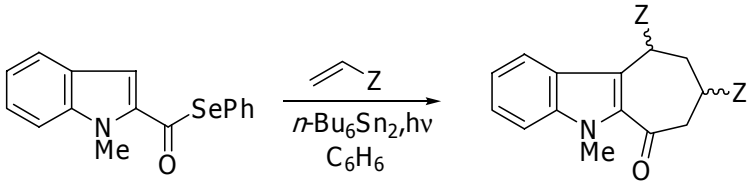
79 **80**

Hiremath *et al*.[57] described a nitrene-based route to the preparation of the diazepino[5,6-*b*]indole-1,5-diones **82** from the azides **81** in refluxing diphenyl ether. The antibacterial activity again *E. coli* and *S. aureus* showed that amongst the [1,3]diazepinoindoles tested, compound **82** (R= R_1= Cl) was moderately active against both bacterial species.



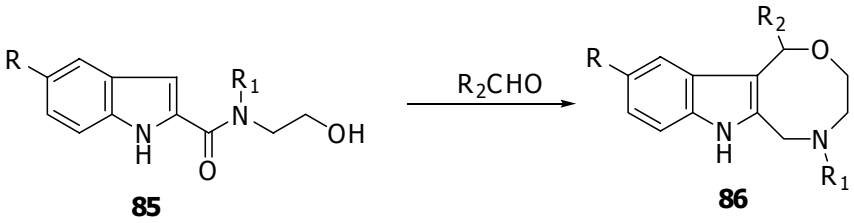
81 **82**

Free radical reactions have also been used to prepare indole-2,3-fused 7-membered rings. For example, radical addition then cyclisation reactions of **83** with reactive alkenes (*Z*= CN or CO_2Me) resulted in the formation of cyclohepta[*b*]indoles **84** as the predominant products.[58]



83 **84**

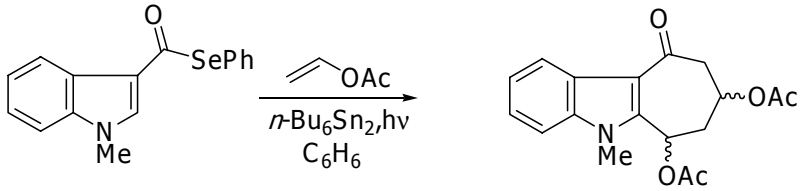
The oxazocinoindoles **86**, which are useful as antihypoxics and antiarrhythmics and contain an indole fused 8-membered ring, were readily accessed via reaction of the indolecarboxamides **85** with aldehydes.[59]



85 **86**

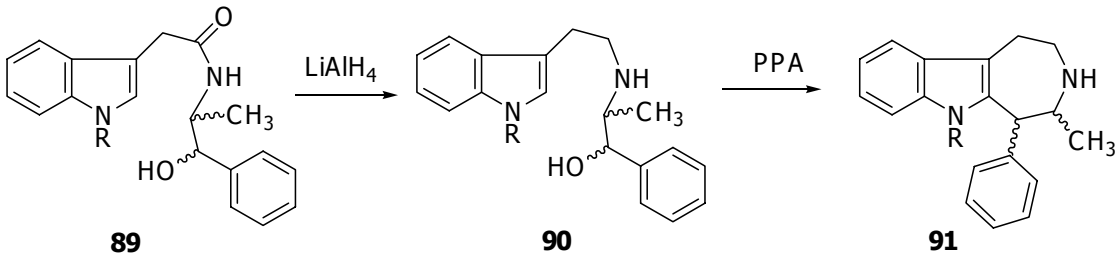
1.3.2.2. Ring closure via 3-substituted indoles

In an analogous reaction sequence to that described for **83**, the 3-indolylacyl radical derived from the selenol ether **87** added to electron rich alkenes to give the cyclohepta[*b*]indole derivative **88**, together with the five-membered ring fused product from the incorporation of one vinyl acetate unit.[60]



87 **88**

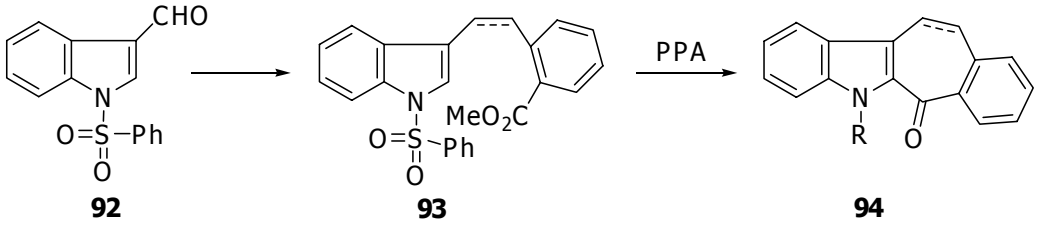
The racemic reduced azepino[4,5-*b*]indoles **91** were prepared by acid-catalysed electrophilic cyclisation with polyphosphoric acid from the precursors **90**, which were obtained in turn from reduction of the amides **89**.[61]



89 **90** **91**

The synthesis and evaluation of *in vitro* cytotoxic activities of *N*-substituted benzo[5,6]cyclohepta[*b*]indole derivatives **94** have also been reported. Wittig coupling provided access to the intermediates **93** from **92**, and the former were then cyclised to C-2

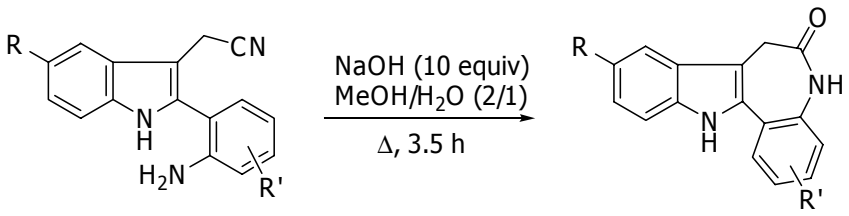
by reaction with PPA. The cytotoxic activities against L1210 murine leukemia and HT29 cell lines showed that compounds **94** have potent antitumour activity in L1210 cell lines.[62]



92 **93** **94**

1.3.2.3 Ring closure via 2,3-disubstituted indoles

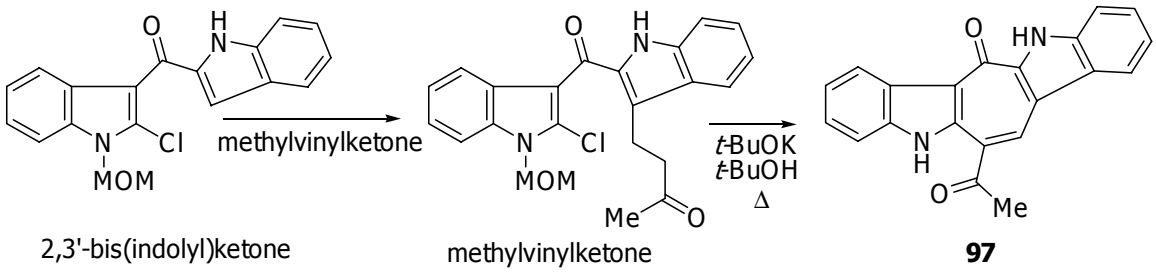
A new family of benzazepinones, the paullones **96**, exhibit potent, ATP-competitive, inhibition of cell cycle regulating cyclin-dependent kinases (CDKs);[63] one such paullone, 9-nitro-7,12-dihydro[3,2-*d*][1]benzazepin-6(5*H*)-one **96** (R= NO_2, R′= H) has progressed to clinical trials. Approximately forty paullones have been studied and features for activity determined. These paullones can be made by cyclisation of a 2,3-disubstituted indole. For example, the paullone **96** (R, R′= H) was prepared by cyclisation of **95** (prepared in turn by borylation/Suzuki coupling technology) under basic conditions.[64]



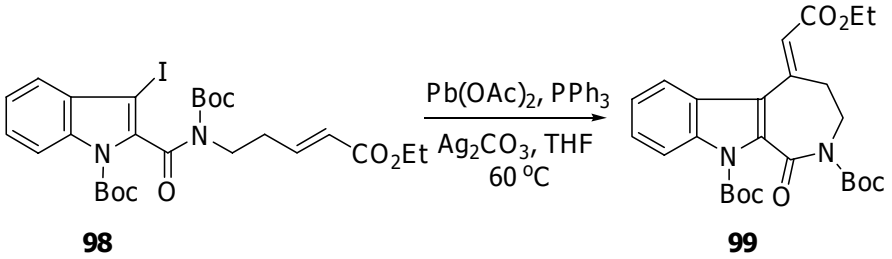
95 **96**

The new bis-indole bearing a functionalised seven-membered ring between the two indole moieties, caulersin[65] **97**, was isolated from the alga *Caulerpa serrulata* from the Xisha Islands in the South China Sea. The synthesis of caulersin **97** has been described[66] and the construction of the seven-membered ring was based on a Michael-type addition

of 2,3′-bis(indolyl)ketone to methylvinylketone followed by an intramolecular nucleophilic substitution and oxidation.

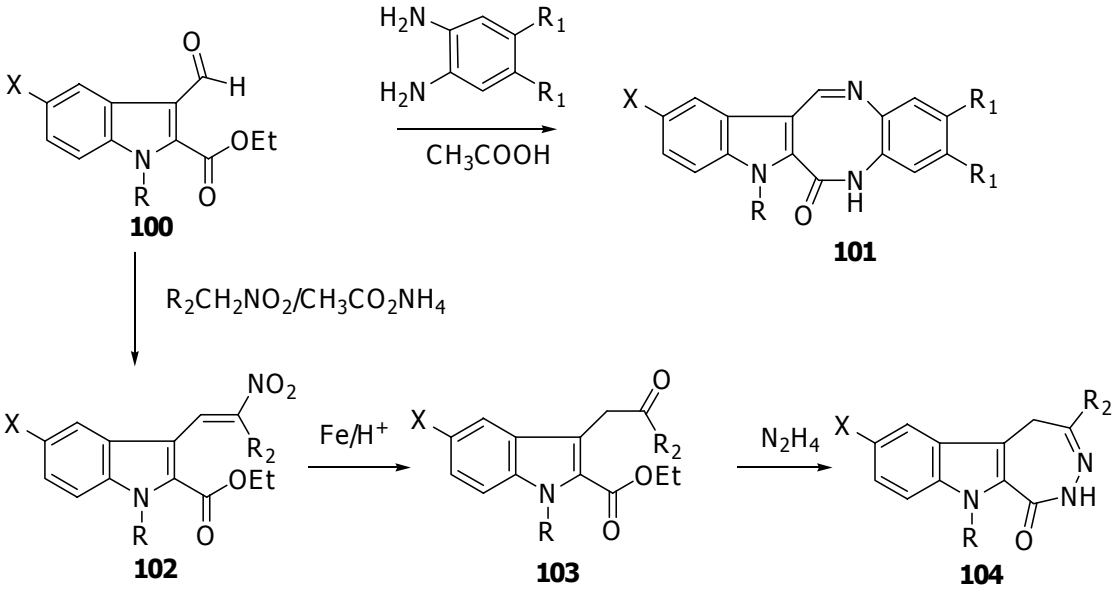


Structures containing azepino[3,4-*b*]indole moieties are of considerable chemical and pharmaceutical importance. A concise approach to these systems (eg. **99**) has been described, based on an intramolecular palladium-mediated cross-coupling reaction.[67]

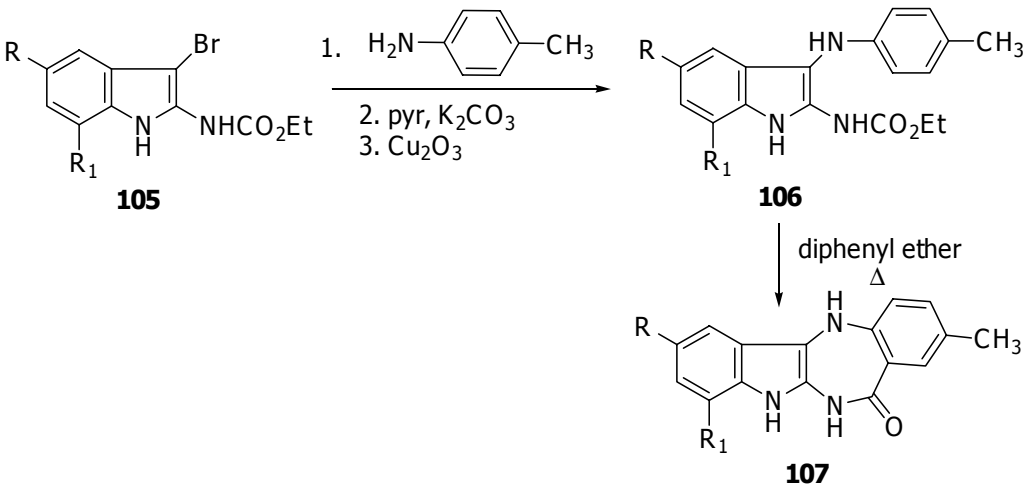


While reports on indole 2,3-fused eight-membered ring systems are less common in the literature, the diazocino[6,7-*b*]indoles **101** (and the diazepinoindoles **104**) have been accessed via the aldehyde indole esters **100**.[68] Reaction of **100** with *o*-phenylenediamine in glacial acetic acid resulted in the fused diazocinoindole system **101**. However, the reaction outcome was not satisfactory and only a low yield of **101** was obtained. Condensation of **100** with an excess of the nitroalkane, followed by reductive hydrolysis of the resulting nitrovinylindoles **102**, gave the substituted indoles **103**, which after treatment with hydrazine then gave the diazepinoindoles **104**[68,69] in satisfactory yields. In the biological

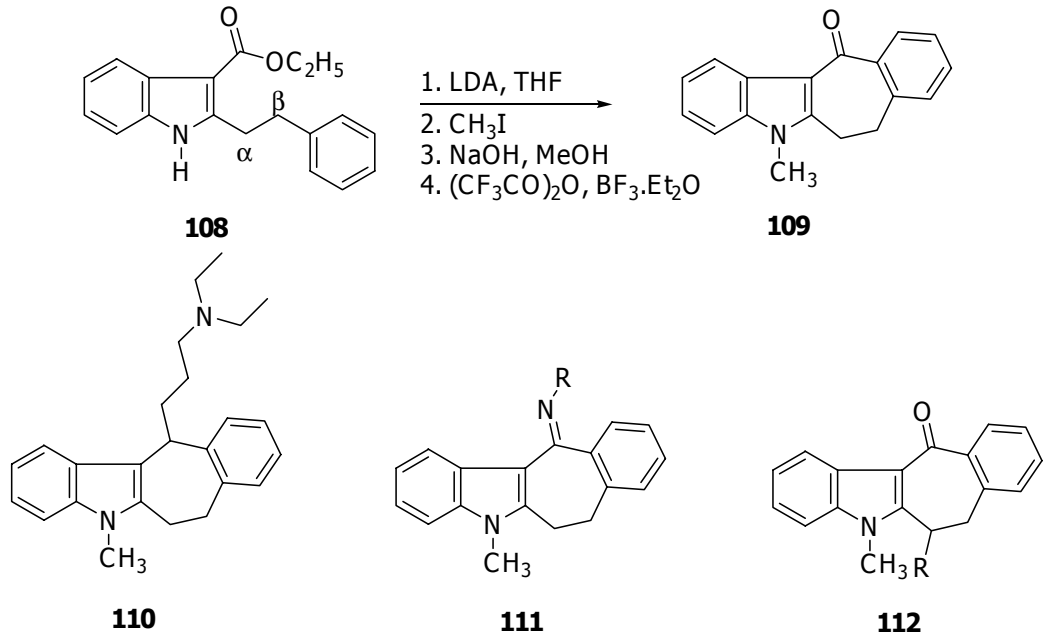
assay of compounds **104** for toxicity using male wistar mice other activities were noted which showed that these compounds could be of interest as potential tranquilising drugs.[69]



Various substituted indolo[3,2-*b*][1,4]benzodiazepines **107**[57] have also been made by cyclisation of the substituted indoles **106**, obtained from the Ullmann reaction of **105** with substituted anilines followed by thermally induced cyclisation of the carbamates **106** to afford compounds of type **107**.

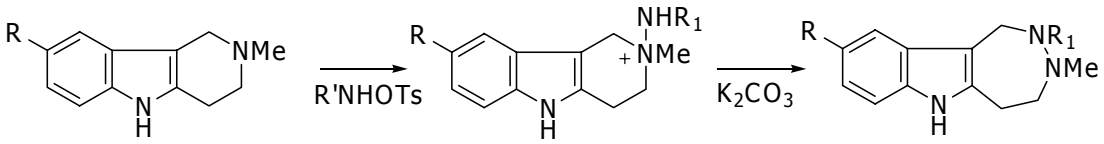


In the continuing search for antitumour drugs, 6,7-dihydrobenzo[4,5]-cyclohepta[1,2-*b*]indol-12(5*H*)-one **109**,[70] a compound with potent antitumour activity, was prepared from the electrophilic cyclisation of indole 3-carboxylate **108** in the presence of trifluoroacetic anhydride and boron trifluoride diethyl etherate. Preparation of the related substituted derivatives **110**-**112** by functionalisation of the ketone **109** has also been reported.[71,72] Unfortunately, the cytotoxicity of these derivatives was significantly less than the reference compound adriamycin.



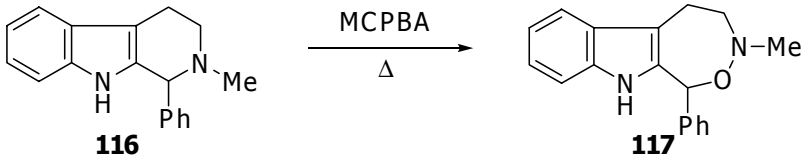
1.3.2.4 Ring expansion routes to fused indoles

A novel ring expansion reaction has been described to prepare the diazepinoindoles **115**. Using *N*-methyl-*O*-tosyl-hydroxylamine, the carbolines **113** were transformed into the diazepinoindoles **115** via the *N*-methylammonium salts **114** in good yields using potassium carbonate in refluxing ethanol.[73]



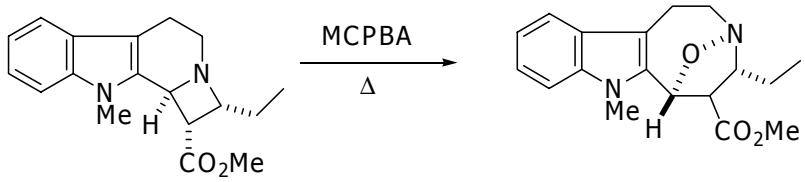
113 **114** **115**

A related thermal Meisenheimer rearrangement of *N*-oxide has been extended to the preparation of fused oxazepine and oxazocine derivatives. For example, the oxazepinoindole **117** was synthesised in good yield by melt pyrolysis, or pyrolysis in ethanenitrile, of the corresponding *N*-oxide from **116**.[74]



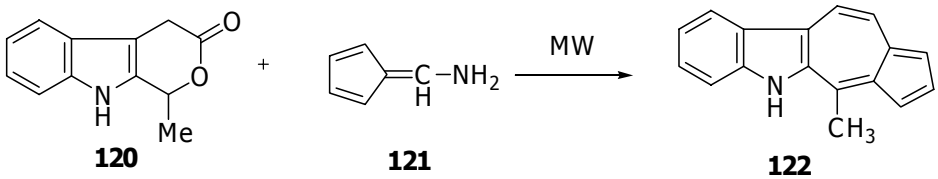
116 **117**

Similarly, the 5-amino-3,6-epoxyhexahydroazocino[5,4-*b*]indole **119** was synthesised from the 2-ethylazetopyridoindole **118** via a Meisenheimer rearrangement of the intermediate *N*-oxide.[75]



118 **119**

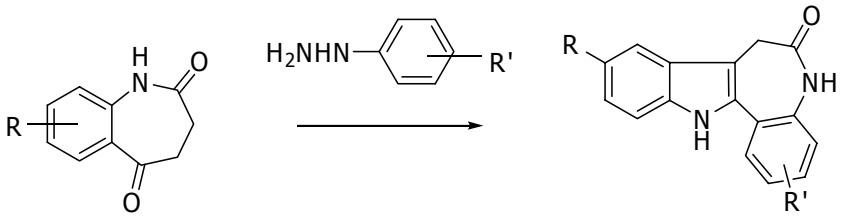
The indole fused seven-membered ring derivative **122** has been synthesised using a microwave-assisted [6+4]-cycloaddition between 6-aminofulvene **121** and the pyrone **120** followed by CO_2 extrusion. This compound **122** displayed good activity against a number of cancer cell lines with average IC_{50} values ranging between 2.2 and 5.4 μM.[76]



120 **121** **122**

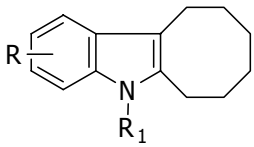
1.3.2.5 Indole ring formation

The synthesis of the paullones **96** (Section 1.3.2.3) can also be achieved by the Fischer indolisation approach from a pre-formed benzazepinedione.[77]



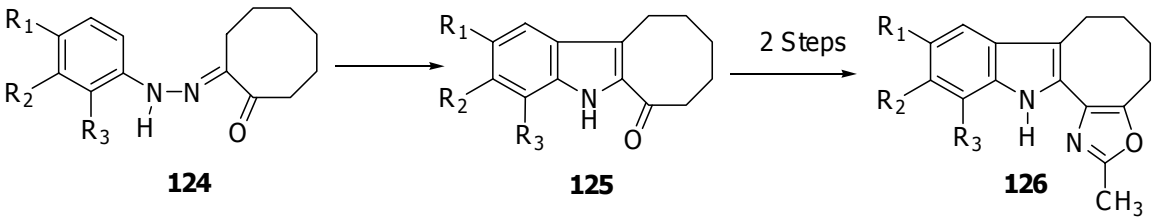
96

Iprindole, a cyclooct[*b*]indole **123** (R= H, R_1= $(CH_2)_3NMe_2$) is a typical tricyclic anti-depressant currently in clinical use,[78] and at high doses it also possesses anti-arrhythmic activity. A series of functionalised iprindole were synthesised in order to examine their potential anti-arrhythmic activity and, with **123** (R= 1-$NHCO_2(CH_2)_2NEt_2$ and R_1= $(CH_2)_3NMe_2$), greater anti-arrhythmic activity was observed than that of iprindole.[79]



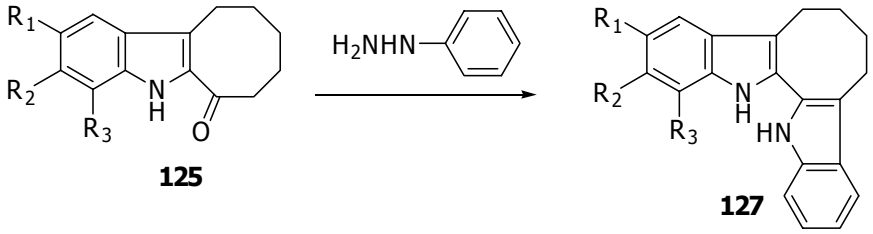
123

Further eight-membered ring fused analogues include the oxazole fused compounds of type **126**. These compounds have also been synthesised via Fischer indolisation in the key initial step to afford **125** from **124**. A further two steps (reactions with hydroxylamine hydrochloride and acetyl chloride) were then necessary to access the oxazole.[80]



124 **125** **126**

Another related series that has been described includes the bis-indole fused derivatives **127** incorporating an eight-membered ring. Fischer indolisation of **125** with phenyl hydrazine in acetic acid afforded **127** in good yield.[81]



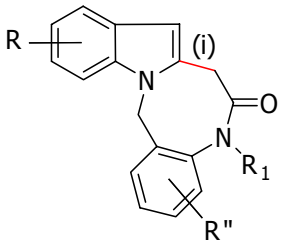
125 **127**

1.4 Aims of the project

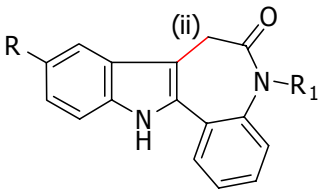
From the survey of the literature on 1,2- and 2,3-fused indoles with seven- or eight-membered rings, it was apparent that considerable further scope existed for new synthetic methodology development, particularly with regard to indole fused eight-membered ring systems. It was also clear that any novel derivatives produced could be of significant interest in terms of bioactivity. The overall aim of this project was to examine new approaches to such systems based on cyclisation onto the indole ring from a 1- or 2-substituted indole derivative. The use of haloacetamide chemistry was to be a key underlying theme. Biologically, we were also interested in examining the antibacterial and antimalarial activities of some of the new compounds.

Therefore, the specific aims of this project were:

- To develop efficient new synthetic routes to the indole-fused eight (**29**) and seven membered (**96**) ring systems by C-C bond formation from the indolic precursors. The carbon-carbon bonds which were to be formed are indicated by bonds (i) and (ii) for **29** and **96**, respectively.

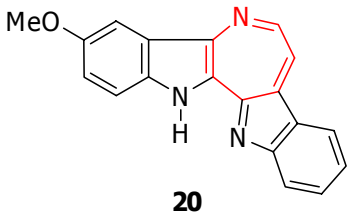


29



96 Paullones

- To synthesise iheyamine A **20**, a novel bis-indole fused seven-membered ring compound from the colonial ascidian *Polycitorella* sp., by a direct and efficient route which would allow the synthesis of new analogues with various substitutents.



20

- To assess the antibacterial and antimalarial properties of the new compounds produced.

1.5 Thesis outline

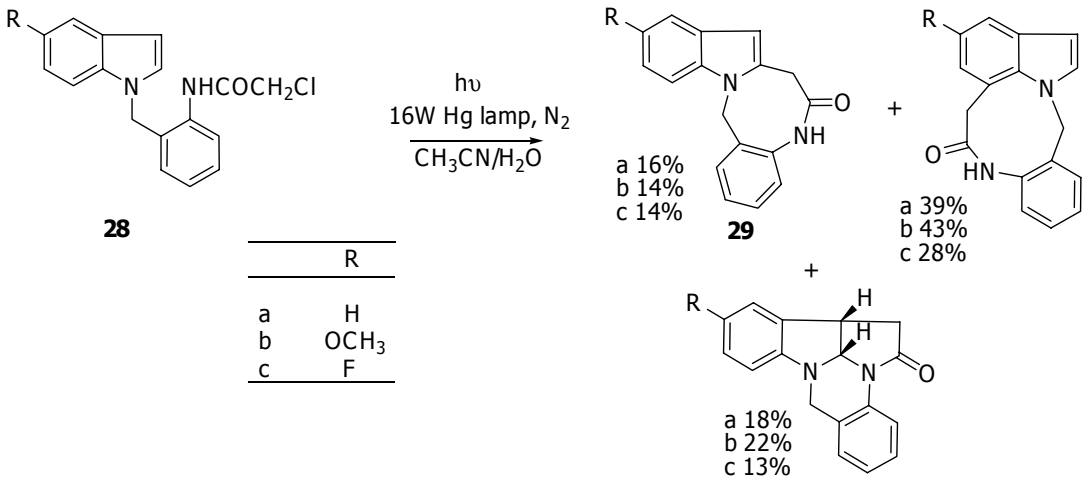
The synthesis of the indole fused eight-membered ring derivatives is discussed in Chapter 2. The synthesis of indole fused seven-membered rings using free radical cyclisation from iodoacetamide precursors is discussed in Chapter 3. Chapter 4 describes

the synthetic approach to iheyamine A, utilising a new rearrangement of a spirocyclic intermediate. Chapter 5 is concerned with the antimicrobial assay results for some of the novel compounds synthesised, while Chapter 6 presents conclusions and future directions. Chapter 7 covers all the experimental details.

2 Indole-fused eight membered ring heterocycles

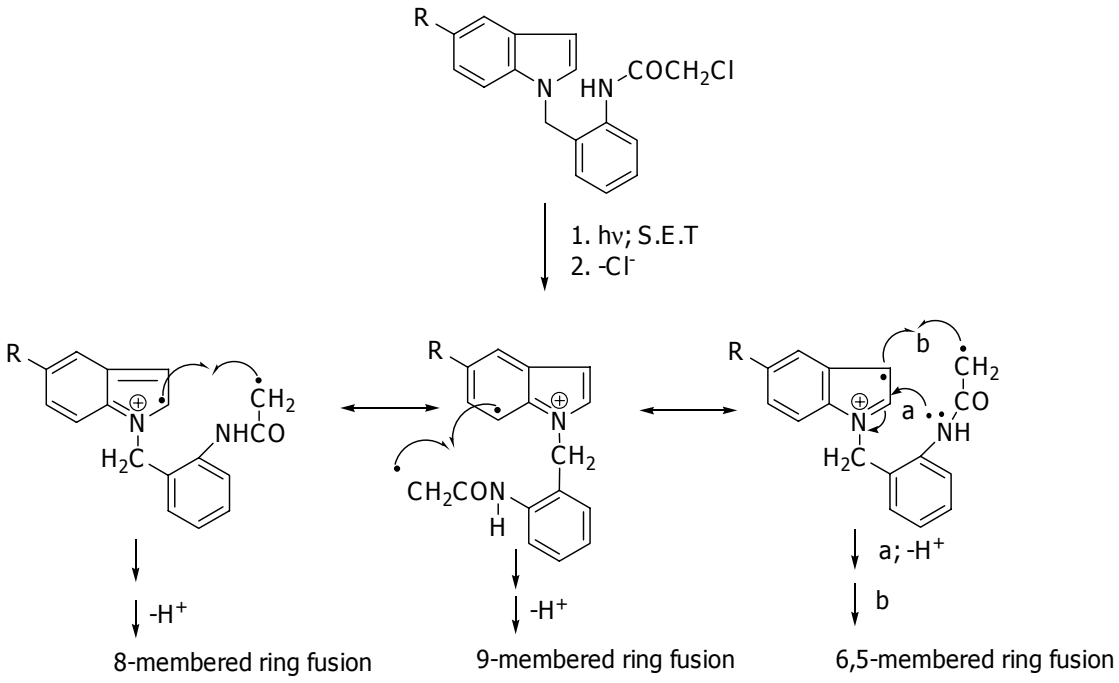
2.1 Introduction

As part of a wider program to identify structurally novel antibacterial compounds with, hopefully, new modes of action to combat resistance problems, we became interested in the indolo[2,1-*d*][1,5]benzodiazocinones **29**, with an indole fused eight-membered ring system. Previous studies in our laboratory had revealed that this system could be accessed in low yields, together with indolo-benzodiazonine and pyrrolo-indoloquinazolines, by photolysis of the chloroacetamides **28** (Scheme 2-1).[30]



Scheme 2-1. Photolysis of chloroacetamides.[30]

The mechanism leading to the cyclisation products involes photo-induced single electron transfer (S.E.T.) with subsequent loss of the chloride ion. The resonance stabilised intermediate may then undergo cyclisation via three pathways as shown in Scheme 2-2.



Scheme 2-2. Mechanism of photocyclisation.

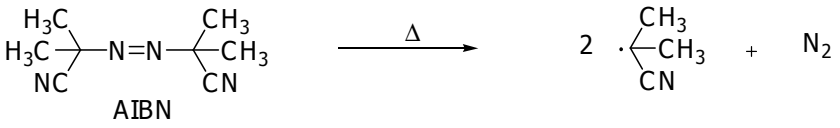
In an effort to develop a viable regioselective route to the indolo-benzodiazocines **29**, free radical cyclisation was of considerable interest. It would be closely related to the photocyclisation, however, only a radical from the precursor 1-indolyl haloacetamides would be involved. This carbon radical from C-X bond cleavage could then undergo cyclisation via an 8-*exo*-*trig* process to give preferentially the indolo-benzodiazocines **29** through attack at C-2. Alternative attack at C-7 would involve disruption of the benzene ring aromaticity and would thus be less favoured.

2.2 Free radical cyclisation

Free radical cyclisation is now an increasingly employed and well established methodology in heterocyclic chemistry.[82-84] The more successful intramolecular radical cyclisations proceed to form five membered rings,[85-87] and these are more general than

those forming six-membered[88] or seven-membered[33,89,90] rings. However, cyclisation leading to indole fused eight-membered rings is less well investigated.

The reaction conditions generally involve the use of excess of tributyltin hydride (Bu_3SnH) with a small equivalent (10-25 mol %) of a radical initiator, most commonly 2,2′-azobisisobutyronitrile (AIBN) because of its high decomposition ability and stability. A variety of solvents can be used but aromatic solvents such as benzene or toluene are the most common.[91] When heating begins, AIBN is decomposed to the $(CH_3)_2C^{\cdot}CN$ radical and nitrogen (Scheme 2-3), which then leads to abstraction of a hydrogen atom from the weak tin-hydrogen bond of Bu_3SnH.

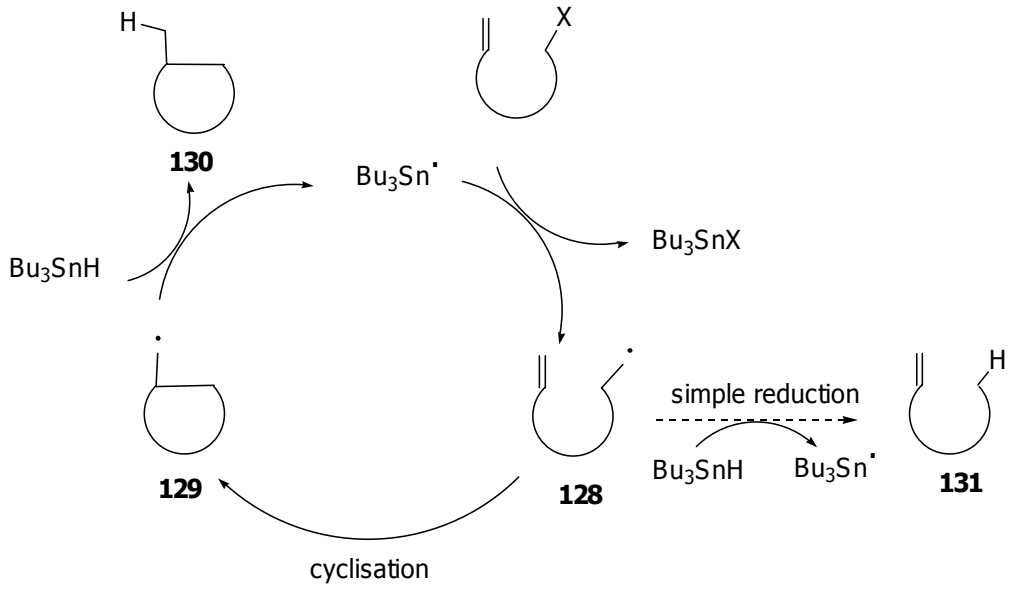


Scheme 2-3. Decomposition of AIBN on heating.

Once the tributyltin radical ($Bu_3Sn^{\cdot}$) is formed, it can react rapidly with a wide range of organic compounds including selenides, sulfides, xanthates and most importantly alkyl halides.[92] *N*-Haloamides have also been widely used for the syntheses of a variety of the nitrogen-containing heterocycles.[85,93-95] Abstracting a halogen atom by $Bu_3Sn^{\cdot}$ is straightforward, leading to the formation of carbon-centred radical **128** (Scheme 2-4). The cyclisation of the carbon-centred radical onto the double bond leads to new carbon-carbon bond formation followed by production of a new carbon-centred radical **129** and then the desired cyclised product **130**.

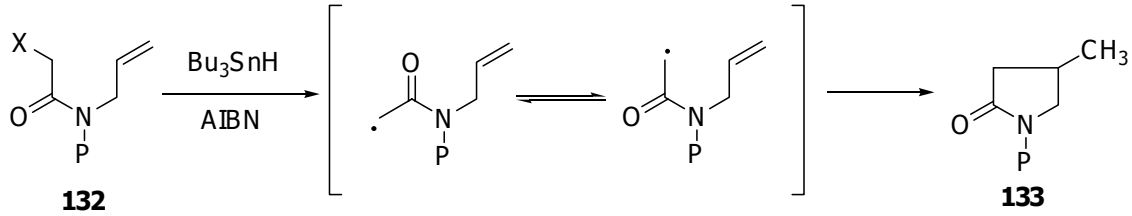
However, an important competitive process is the simple reduction of the carbon-centred radical **128** with Bu_3SnH leading to the unwanted compound **131**. To avoid this, it

is usually carried out by controlling the concentration of the Bu_3SnH (slow addition of tin hydride and/or use highly dilute solution of Bu_3SnH).[88,91]



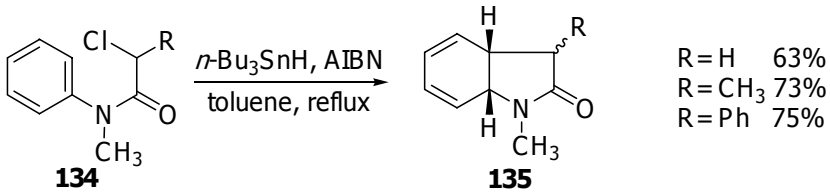
Scheme 2-4. Transformation of unsaturated halides to cyclic products using Bu_3SnH.[92]

Most radical cyclisations used for the syntheses of heterocycles proceed by 5-*exo-trig* regioselectivity, especially the pyrrolidinones **133**. Cyclisations of a variety of secondary haloamides **132** often give excellent yields when using a large bulky nitrogen protecting group (P).[96]



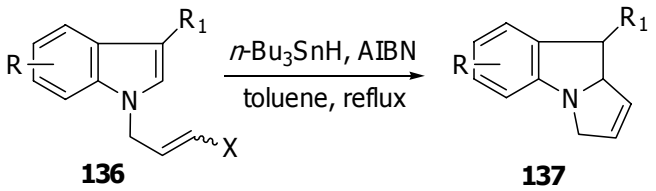
Scheme 2-5. Radical cyclisation via 5-*exo-trig* regioselectivity.

However, the radical cyclisation via the disfavoured *5-endo-trig* process of *N*-vinylic α-chloroacetamides **134** has also been achieved to give the five-membered ring lactams **135** in good yields (Scheme 2-6).[97]



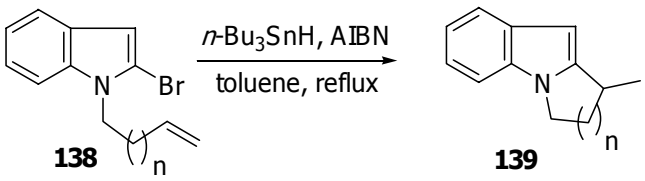
Scheme 2-6. Radical cyclisation of α-chloroacetamides 134.

Cyclisations involving indole ring systems have also proved to be useful synthetically. The terminal vinyl radicals, generated from vinyl halides **136** using Bu_3SnH, have been cyclised onto the indole 2-position to yield dihydroindoles **137** in fair yields (Scheme 2-7).[98] No evidence was reported for the C-7 cyclisation.



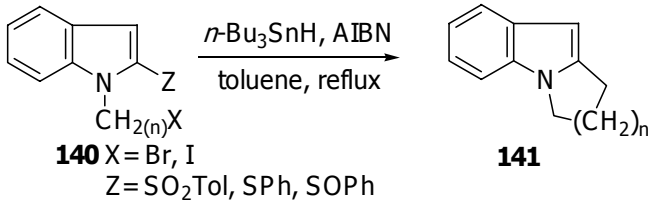
Scheme 2-7. Cyclisation of vinyl radicals onto indole rings.

Another useful method for cyclisation at the 2-position of indoles involved the use of the *N*-alkenyl-2-bromoindole precusor **138**[99] and Bu_3SnH. The indol-2-yl radicals generated undergo *5-exo* (n= 1) and *6-exo* (n= 2) cyclisation to yield the corresponding cyclised indole derivatives **139**.



Also, (*N*-bromo and *N*-iodoalkyl)indoles, substituted in the 2-position by benzenesulfanyl, benzenesulfinyl and 4-(methylphenyl)sulfonyl groups **140**, undergo *ipso* aromatic homolytic substitution to yield fused [1,2-*a*]indoles **141**.[100,101] The cyclisation of

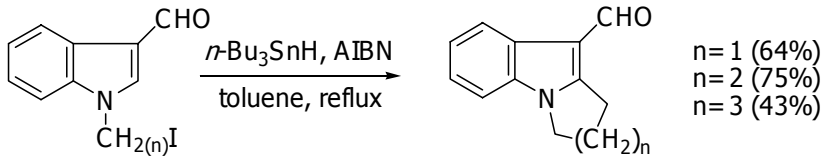
N-alkyl radicals onto the 2-position of the indoles afforded the intermediate indole π-radical which then rearomatised with expulsion of the benzenesulfenyl, benzenesulfinyl or 4-(methylphenyl)sulfonyl groups.



140 X = Br, I
Z = SO_2Tol, SPh, SOPh

141

Moody *et al.*[33] have described an alternative route to the systems above by cyclisation of 1-(ω-iodoalkyl)indole-3-carbaldehydes **142**. This procedure involved the generation of alkyl radicals from iodoalkylindoles **142** which then cyclised onto the 2-position of the indole ring. The intermediate radicals produced are stabilised by the 3-carbaldehyde, and are then aromatised by an oxidative process.[33]



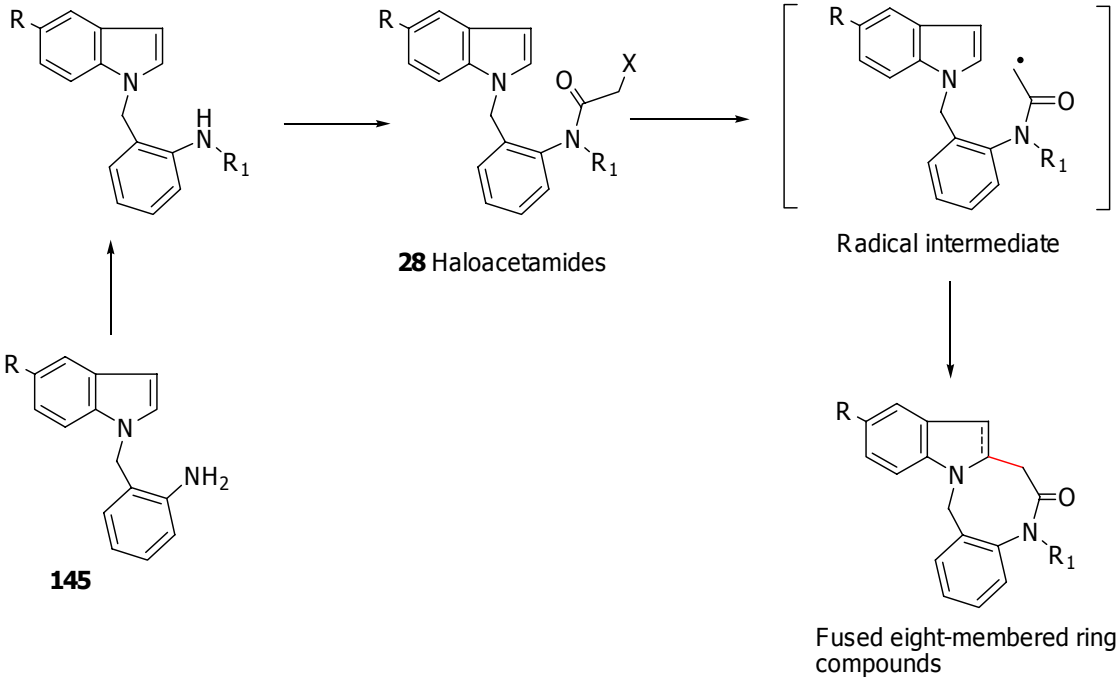
142 **143**

The sucessful production of fused [1,2-*a*]indoles via radical cyclisation onto indole rings suggested that amidylmethyl radicals, generated from haloacetamides, would be of value in the cyclisation onto the indole ring to give indole fused eight-membered ring compounds.

The initial goal of the work described here was to investigate the cyclisation of haloacetamides **28** via an 8-*exo*-*trig* process to give only the indolo-benzodiazocines **29**.

2.2.1 Proposed synthetic approach to indole fused eight-membered rings

The synthetic approach involved an intramolecular free radical cyclisation reaction of *N*-substituted haloacetamides (Scheme 2-8). The haloacetamides could be prepared as described by Bremner *et al*.[30] by haloacetylation of a secondary amine, *N*-substituted with an alkyl or acyl group (R_1). The *N*-substitutents were required to ensure conformational control for cyclisation. After cyclisation, removal of this substituent group (R´) was planned to afford the secondary lactam derivatives.

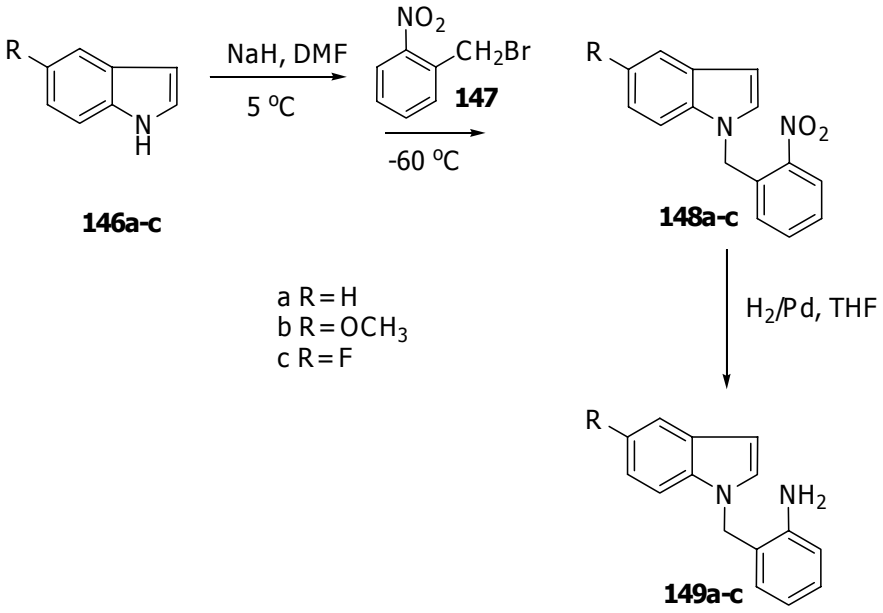


Scheme 2-8. Proposed synthetic approach to indole fused eight-membered ring compounds.

2.2.2 Preparation of amine starting materials (145)

The precursors for the cyclisation were prepared following the method used in Bremner *et al*,[30] starting from the 1*H*-indoles **146**. These indoles were *N*-alkylated using 2-nitro benzylbromide **147** followed by nitro group reduction to yield the respective anilines

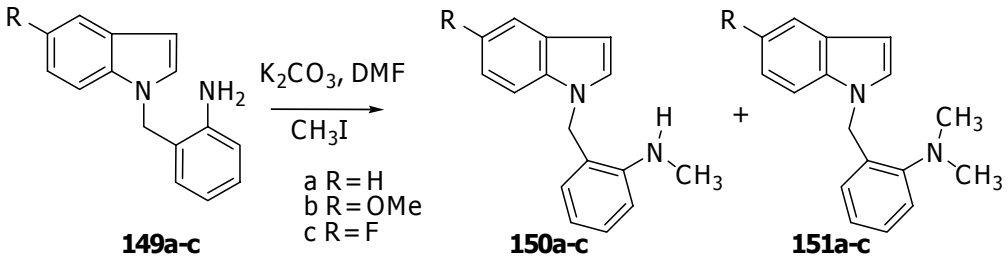
149 (Scheme 2-9). These compounds were identified by MS and ^{1}H NMR and by comparison[30] with the literature data. Alkylation or acylation of the anilines **149a-c** was then investigated.



Scheme 2-9. Preparation of aniline starting materials 149.

2.2.3 *N*-methylation of primary amines

N-Methylation of the anilines **149a-c** was conducted using the direct approach of reacting the amines with methyl iodide at room temperature (Scheme 2-10). Both mono- and di-methylated products were obtained from this reaction, but the two could be separated. The resultes are shown in Table 2-1.



Scheme 2-10. *N*-methylation reaction.

Treatment of 1-[(2-aminophenyl)methyl]1*H*-indole **149a** with 1.1 equivalents of methyl iodide gave a fair yield of the monomethylated product **150a**, but with a considerable amount of starting material remaining. On increasing the amount of methyl iodide to 1.5 equivalents, the yield of the monomethylation product **150a** was increased to 42%, however, the dimethyl amine **151a** was also then observed. On treatment with a large excess of **149a**, the yield of **150a** increased to 90% with respect to methyl iodide, however, a large amount of starting material was also recovered.

The *N*-methylation of **149b** gave 71% of the monomethylated product **150b** and 36% of the starting material together with some comtaminants (determined by ^{1}H NMR spectroscopy) when using 1.1 equivalents of methyl iodide. When the equivalents of the methyl iodide increased, the yield of the monoalkylation product did not improve, and the dimethyl derivative **151b** was also obtained. Even when the large excess of the aniline was used, the yield of the monomethylated product dropped to 40% with respect to methyl iodide. In the case of the *N*-methylation of **149c**, only dimethylated product **151c** was obtained when using 1.1 equivalents of methyl iodide.

The structural elucidations of the methylation products were based on spectroscopic data. The ^{1}H NMR spectra of the mono-methylated products **150a-b** showed a singlet integrating for three protons ascribed to the methyl group at about 2.74 ppm and a broad singlet signal ascribed to the NH proton at about 3.51 ppm. Evidence for the dimethylated products **151a-c** was also observed in the ^{1}H NMR spectra, with a singlet of six protons ascribed to the two methyl groups at about 2.74 ppm as well as the absence of the broad singlet for the NH proton.

Table 2-1. *N*-methylation of anilines 149 with methyl iodide

Entry	Substrate **149** (eq.)		MeI (eq.)	Yields (%)		Unreacted **149** (%)
				150	**151**	
1	a	1	1.1	31	-	48
2		1	1.5	42	27	16
3		5	1	90[a]	-	79
4	b	1	1.1	71	-	36[b]
5		1	1.5	19	23	37
6		5	1	40[a]	-	66
7	c	1	1.1	-	100	-

[a] calculated with respect to methyl iodide [b] not pure

While direct *N*-alkylation of primary amines with alkyl haildes is the most common and straightforward route to substituted amines, this method is limited due to the possibility of multiple alkylation giving rise to mixtures of primary, secondary, and tertiary amines as well as quaternary ammonium salts.[102] Once the amine has been alkylated to the monoalkyl derivative (step II), the molecule is more susceptible to further alkylation, and thus the dialkyl derivative is formed much faster than the remaining primary amine is alkylated (Figure 2-1). With an excess of the starting material, the monoalkylation products are predominantly obtained.[102-104]

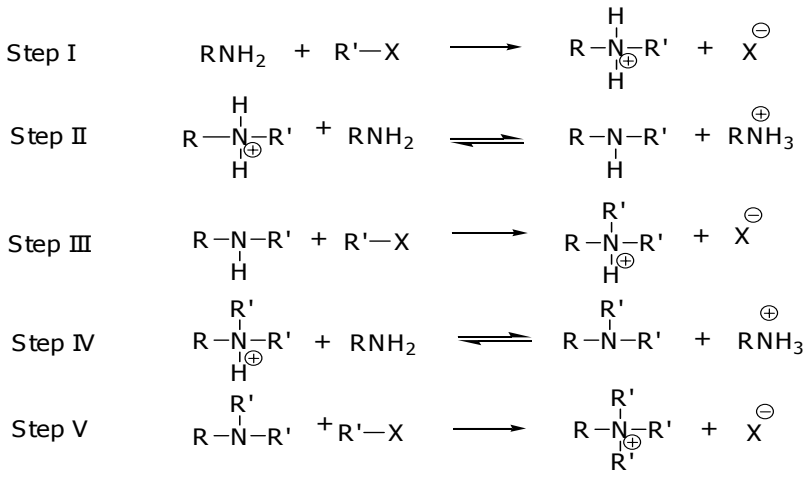
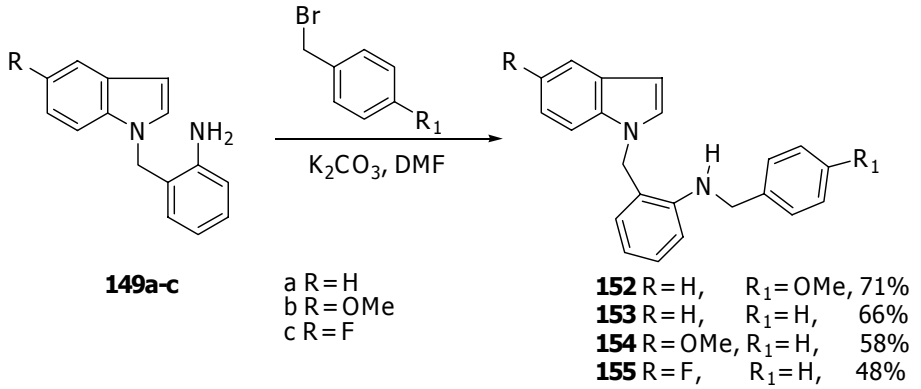


Figure 2-1. Mechanism of direct *N*-alkylation.

2.2.4 *N*-benzylation of primary amines

When the amines **149a-c** were alkylated with 4-methoxybenzyl bromide or benzyl bromide (1:1 equivalents), no dialkylated products were observed (Scheme 2-11). The ^{1}H NMR spectrum of the reaction mixture of **152** showed a singlet at 3.86 ppm ascribed to the amine NH and a 3-proton singlet at 3.88 ppm, ascribed to the methoxy group. The presence of a singlet resonating at 4.26 ppm was seen for the benzylic protons, together with four extra protons in the aromatic region, indicated the addition of the *p*-methoxybenzyl group onto the starting material. Similarly, the ^{1}H NMR spectrum of the reaction mixture for **153** showed singlets at 3.93 and 4.32 ppm ascribed to the amine NH and benzylic protons, respectively, together with signals consistent with some starting material being present. After purification by flash chromatography, the pure products were obtained in 71% and 66% yield for **152** and **153**, respectively. The lack of *N*,*N*-dialkylation in these cases is probably due to steric hinderance in the second alkylation step with the more bulky alkylating agents. The same results were obtained in the preparation of 1-[(2-

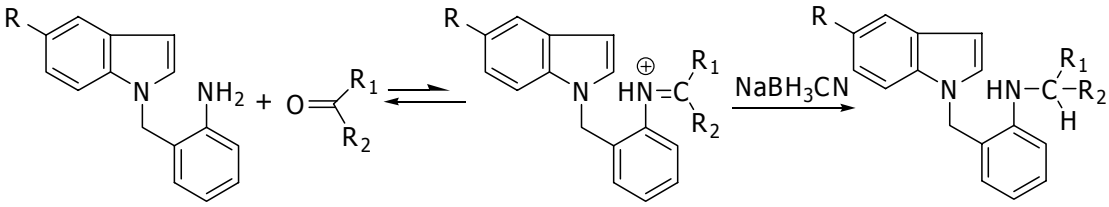
aminophenyl)methyl]-5-methoxy-1*H*-indole **154** and 1-[(2-aminophenyl)methyl]-5-fluoro-1*H*-indole **155**; these *N*-benzylated products were isolated in 58% and 48% yield respectively, and no dialkylation products were observed (Scheme 2-11).



Scheme 2-11. *N*-benzylation of primary amine.

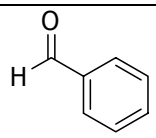
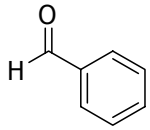
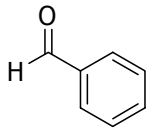
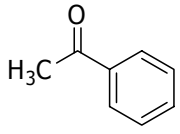
2.2.5 Reductive amination

An alternative to *N*-alkylation using the reductive amination method was also investigated in this stage of the work. With sodium cyanoborohydride as a reducing agent,[105] it has been shown that reductive amination of aldehydes and unhinderded ketones with ammonia, primary and secondary amines, provides efficient access to *N*-alkylamines. This procedure was then applied to the condensation of amines **149a-c** with various aldehydes to give the iminium salt, which was then reduced *in situ* by sodium cyanoborohydride to give the *N*-alkylamines (Scheme 2-12). The results are shown in Table 2-2.



Scheme 2-12. Reductive amination of primary amines.

Table 2-2. Reduction amination of the amines 149a-c using $NaBH_3CN$ in methanol.

Entry	Aniline	Aldehyde or Ketone (equivalents)	Product (yield, %)	
			Monoalkylation	Dialkylation
1	**149a**	 (1)	**150a** (44)	**151a** (25)
2	**149a**	 (1)	**153** (66)	-
3	**149b**	 (1)	**154** (28)	-
4	**149c**	 (1)	**155** (21)	-
5	**149a**	 (0.2)	**156** (74) (R= H, R_1= CH_3, R_2= Ph)	-

Even using reductive amination for the *N*-methylation of 1-[(2-aminophenyl)methyl]-1*H*-indole **149a**, some dimethylated product **151a** (25%) was still obtained from further reaction of **150a** with formaldehyde. When 1-[(2-aminophenyl)methyl]-1*H*-indole **149a** was treated with 1 equivalent of benzaldehyde in the presence of $NaBH_3CN$, **153** was obtained in 66% yield and no dialkylated product was observed. The yield of **153** was similar to that obtained from the direct *N*-alkylation approach. However, reductive amination of 1-[(2-aminophenyl)methyl]-5-methoxy-1*H*-indole **149b** or 1-[(2-aminophenyl)methyl]-5-fluoro-1*H*-indole **149c** using the same reaction conditions as for **149a**, gave only 28% and 21% of the {1-[(2-*N*-benzylaminophenyl)methyl]}-5-methoxy-1*H*-indole **154** and {1-[(2-*N*-benzylaminophenyl)methyl]}-5-fluoro-1*H*-indole **155**, respectively. The lower yields are difficult to explain but may be associated with the larger scale of the reactions compared with the analogous reactions with **149a**.

Treatment of **149a** with 0.2 equivalents of acetophenone in the presence of $NaBH_3CN$, gave a product which on analytical TLC showed two components with similar R_f values. However, mass spectrometry showed only an ion peak at *m/z* 327 $[MH]^+$ corresponding to 1-{[2-*N*-(phenylethyl)aminophenyl]methyl}-1*H*-indole **156**. The ^1H NMR spectrum indicated a 3:1 amide rotamer mixture.

Borch *et al*.[106] noted that when the reductive amination reactions are run using a fivefold excess of the amine, this improves the initial equilibrium to yield the iminiun ion intermediate and also minimises the reaction of product amine with the carbonyl compound. However, with the amines **149a-c**, the molecules are hindred for further reaction with another aldehydes or ketones, therefore, the excess use of the amines might be unnecessary.

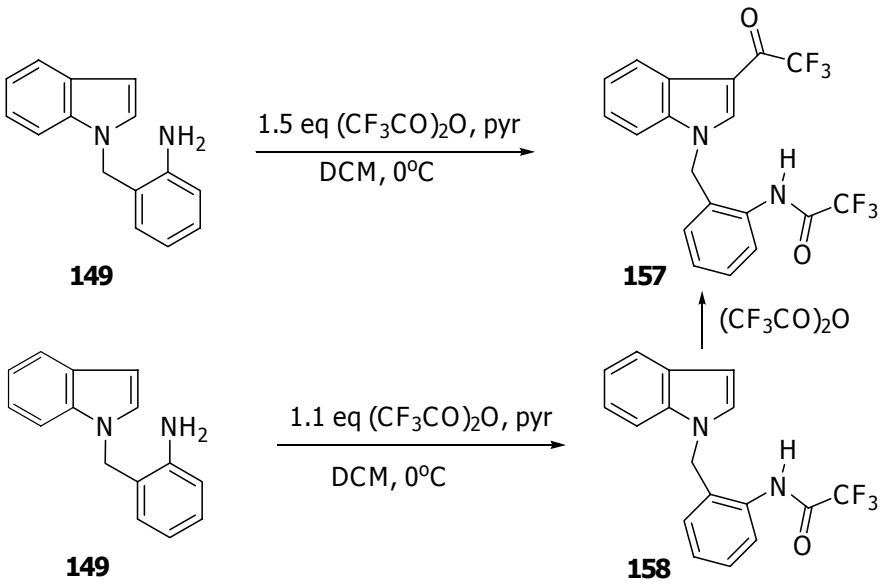
2.2.6 *N*-acylation of primary amine

The most common method for the preparation of *N*-substituted amines is via treatment of a primary amine with acylating agents.[103] Acid chlorides and acid anhydrides are highly reactive acylating agents and react very rapidly with amines. Typically, this reaction is conducted under basic conditions, using bases such as potassium carbonate or sodium hydroxide to generate the free amine base (if required), and deprotonation of the amine nitrogen using a strong base such as sodium hydride.

Trifluoroacetic anhydride was of interest as the reaction is rapid and the *N*-deprotection can occur under mildly basic conditions.[107] However, the trifluoroacetyl group is susceptible to nucleophilic attack and the indole ring is sufficiently reactive at the 3-position to be substituted by electrophiles. Thus, treatment[108] of amine **149a** with 1.5 equivalents of trifluoroacetic anhydride in dichloromethane at 0 ^{o}C gave the *N*-{2-[3-trifluoroacetyl-1-(1*H*-indolyl)methyl]phenyl}trifluoroacetamide **157** in 66% yield. The ^{1}H NMR spectrum of **157** revealed the absence of a singlet proton that could be ascribed to the hydrogen at the 2-position on the indole ring and a broad singlet integrating for one proton, which was assigned to the NH proton at 8.04 ppm. Evidence for the trifluoroacetyl groups was also observed in the ^{13}C NMR spectrum. The signals ascribed to the trifluoroacetyl carbonyl groups resonated at 156.4 and 157.3 ppm. The HREI-MS of **157** gave a peak at *m/z* 414.0780 (M^{+}) consistent with the molecular formula $C_{19}H_{12}N_2O_2F_6$.

Treatment of **149** with 1.1 equivalents of trifluoroacetic anhydride in pyridine gave only the *N*-acylated product **158** in 92% yield. The ^{1}H NMR spectrum clearly showed the presence of ten aromatic protons (6.60-7.64 ppm), which suggested that no trifluoroacetylation of the aromatic core had occurred. The broad signal formerly indicative

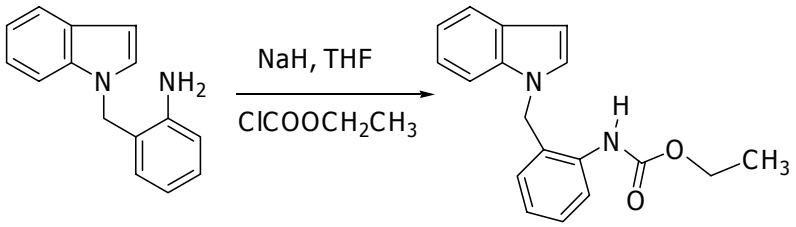
of the amine hydrogens was not present in the ^{1}H NMR spectrum, and the ^{13}C spectrum revealed the presence of a signal assigned to the quaternary CF_3 group at 115.5 ppm and the carbonyl group at 155.5 ppm. In addition, HREI-MS showed a molecular ion at *m/z* 318.0990 consistent with the molecular formula $C_{17}H_{13}N_2OF_3$ and in line with the substitution of a trifluoroacetyl group in the starting material. This suggested that the trifluoroacetyl group was incorporated in the amine nitrogen first, then the excess trifluoroacetic anhydride resulted in electrophilic aromatic substitution at the 3-position of the indolic ring (Scheme 2-13).



Scheme 2-13. Preparation of trifluoroacetamides 157 and 158.

Many carbamates (such as ethyl, methyl, *t*-butyl and benzyl carbamate), have been used as nitrogen protecting groups. Ethyl carbamate was chosen in this case as it can be readily prepared and deprotected.[109] The carbamate protected indole derivatives were prepared using sodium hydride and ethyl chloroformate (Scheme 2-14). The 1-[(2-*N*-ethylcarbamoylaminophenyl)methyl]-1*H*-indole **159** was obtained in near quantitative yield. The structure was identified by NMR and mass spectrometic analysis. The ^{1}H NMR

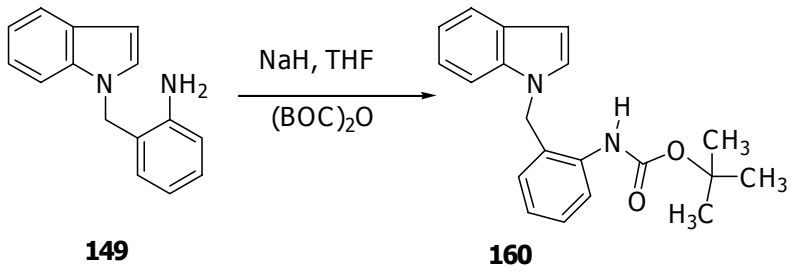
spectrum showed a 3-proton triplet at 1.28 ppm, which was ascribed to the methyl group, as well as a quartet attributed to the CH_2 at 4.20 ppm and a broad singlet integrating for one proton indicative of the NH proton at 6.36 ppm. HRCI-MS gave a peak at *m/z* 295.1446 (MH^+) consistent with the molecular formula $C_{18}H_{18}N_2O_2$, which supported the structure assigned to **159**.



149 **159**

Scheme 2-14. Preparation of *N*-ethylcarbamate 159.

The Boc protecting group is one of the most useful nitrogen protecting groups as it is relatively easy to remove under mild acidic conditions. It was also investigated in this study. Treatment of amine **149** with sodium hydride and Boc anhydride gave the Boc protected compound **160** in 100% yield as orange crystals (Scheme 2-15). The HREI-MS gave a molecular ion at *m/z* 322.1697 consistent with the molecular formula $C_{20}H_{22}N_2O_2$. The ^1H NMR spectrum of **160** showed a singlet at 1.47 ppm, representative of the *t*-butyl group, and a broad singlet at 6.20 ppm consistent with the NH proton. The ^{13}C NMR spectrum showed a resonance at 28.6 ppm ascribed to the methyl carbon, a resonance at 81.0 ppm ascribed to the quaternary carbon of the *t*-butyl group and a resonance at 153.5 ppm ascribed to the carbonyl carbon.

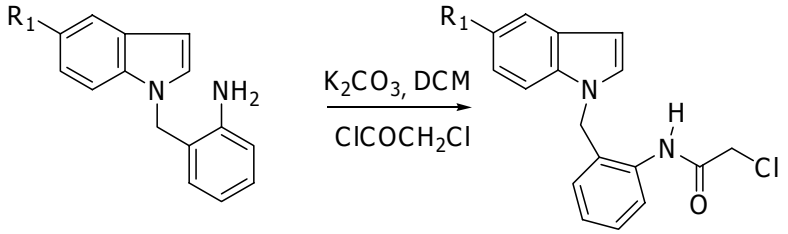


149 **160**

Scheme 2-15. Preparation of *N*-Boc compound 160.

2.2.7 Preparation of chloroacetamides

A general method for preparing the chloroacetamide derivatives was based on the method described by Bremner *et al.*[30] Amines **149a** and **149c** were reacted with chloroacetyl chloride in DCM to give the chloroacetamindes **161** and **162** in 84% and 86% yield respectively (Scheme 2-16). The ^{1}H NMR and ^{13}C spectra of **161** and **162** were identical to those previously reported in the literature.[30] The ^{1}H NMR spectra of both **161** and **162** showed characteristic singlet signals ascribed to the methylene protons of the chloroacetyl moiety at 4.03 ppm and 4.06, respectively. Signals assigned to the corresponding methylene carbons were also observed in the ^{13}C NMR spectra at 42.7 ppm and 43.1 ppm for **161** and **162**, respectively.

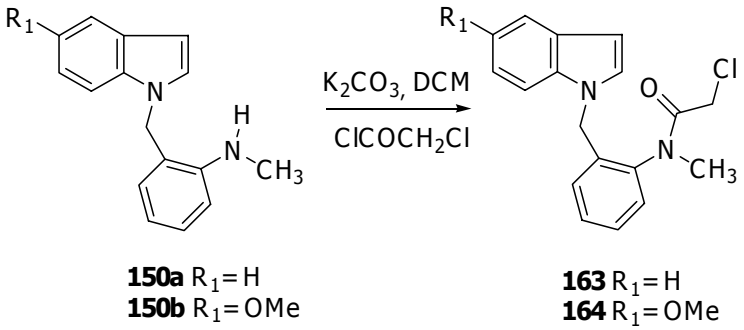


149a R_1 = H
149c R_1 = F

161 R_1 = H
162 R_1 = F

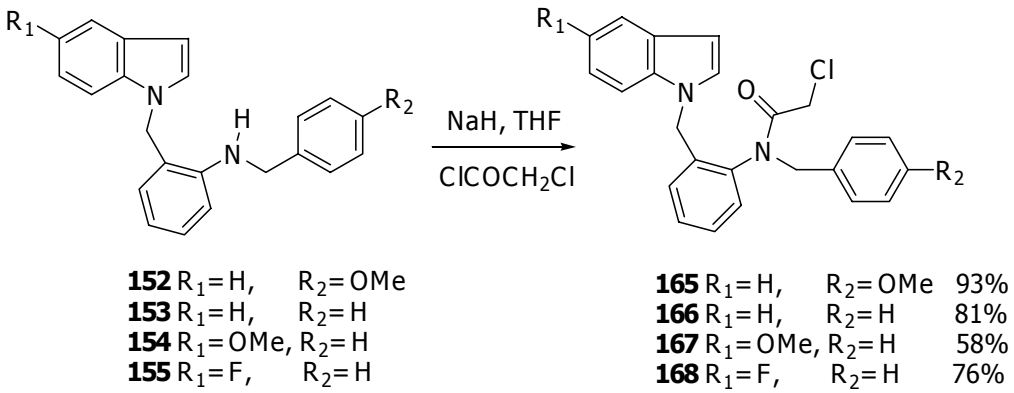
Scheme 2-16. Preparation of *N*-unsubstituted chloroacetamides.

This general procedure was also used for the acetylation of the *N*-alkylamines **150a** and **150b** to afford the *N*-methylchloroacetamides **163** and **164** in 57% and 58% yields, respectively (Scheme 2-17). The products were identified by their ascribed methylene signals in both the ^{1}H NMR and ^{13}C NMR spectra as well as via LRMS and HRMS. In the ^{1}H NMR spectra, the methylene protons of the chloroacetyl moiety were ascribed to two sets of doublets at 3.56 ppm (*J*= 12.6 Hz) and 3.66 ppm (*J*= 12.6 Hz) and the benzylic methylene protons were ascribed to a doublet at around 5.25 ppm. The splitting patterns of the methylene protons suggested hindered rotation around the amide bond in these molecules **163** and **164**. The ^{13}C NMR spectra indicated the presence of the methylene carbon at 41.2 ppm. A signal ascribed to the carbonyl carbon in each case was also observed at 164.6 and 166.8 ppm for **163** and **164**, respectively.



Scheme 2-17. Preparation of *N*-methylchloroacetamides.

In the preparation of the *N*-benzylchloroacetamides **165-168** (Scheme 2-18), deprotonation of the amine nitrogen was achieved utilising a strong base, sodium hydride (NaH), followed by acylation using chloroacetyl chloride to give **165-168** in generally good yields (75-93%). These products were identified by the characteristic signals ascribed to the chloroacetyl methylene signals in both the ^{1}H NMR and ^{13}C NMR spectra as well as via LRMS and HRMS.

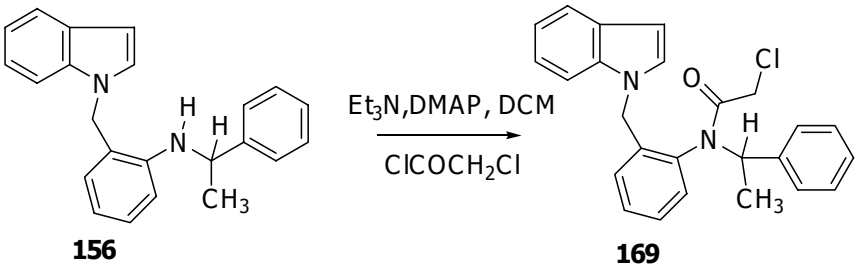


152 R_1=H, R_2=OMe
153 R_1=H, R_2=H
154 R_1=OMe, R_2=H
155 R_1=F, R_2=H

165 R_1=H, R_2=OMe 93%
166 R_1=H, R_2=H 81%
167 R_1=OMe, R_2=H 58%
168 R_1=F, R_2=H 76%

Scheme 2-18. Preparation of *N*-benzylchloroacetamides.

However, treatment of the *N*-phenylethyl amine **156** with NaH and then chloroacetyl chloride gave none of the expected amide product **169,** which was possibly due to the bulky phenylethyl group. The chloroacetamide **169** was obtained in 33% yield when 4-dimethylaminopyridine (DMAP) was used as a acylation catalyst (Scheme 2-19).[94]



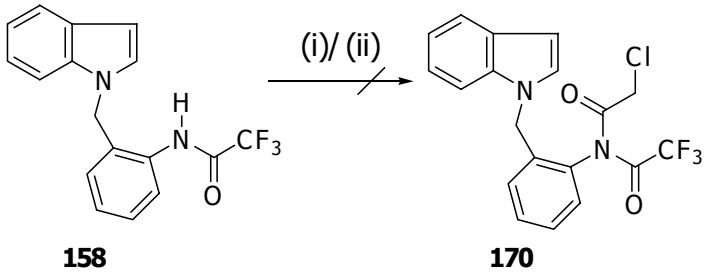
156 **169**

Scheme 2-19. Synthesis of *N*-ethylbenzylchloroacetamide 169.

The dimethylamino moiety in DMAP acts as an electron donor substituent, increasing both the nucleophilicity and basicity of the pyridine nitrogen. This pyridine nitrogen is involved in the initial reaction with chloroacetyl chloride to afford an acyl pyridinium ion intermediate, which is a powerful acylating agent and reacts more rapidly with the amine than chloroacetyl chloride alone. Thus, using DMAP in acylations with

chloroacetyl chloride may increase the acylation rate by up to four orders of magnitude and permits sucessful acylation of hindered amines.[103] With the addition of large groups to the amide nitrogen, the molecule became very bulky and free rotation was reduced. This hindered rotation was confirmed by the ^{1}H NMR and ^{13}C NMR spectra, which showed two rotamers in a ratio of 2:1 (determined by ^{1}H spectroscopy). The ^{1}H NMR spectrum was complicated in the aromatic region. However, two sets of singlet signals were seen at 1.58 ppm and 1.64 ppm and these were ascribed to the methyl group for the minor rotamer and the major rotamer, respectively, as well as four sets of doublet signals, each set being ascribed to the benzylic methylene protons. The HRCI-MS gave a peak at *m/z* 403.1559 (MH^{+}) consistent with the molecular formula $C_{25}H_{24}N_2OCl$ and the addition of the phenylethyl group to the starting material.

The attempted preparation of the amide **170** by chloroacetylation using potassium carbonate in DCM or NaH in THF (Scheme 2-20) was unsucessful, possibly due to the ready hydrolysis of the trifluoroacetyl in **170**. Further investigation of this reaction was not pursued.



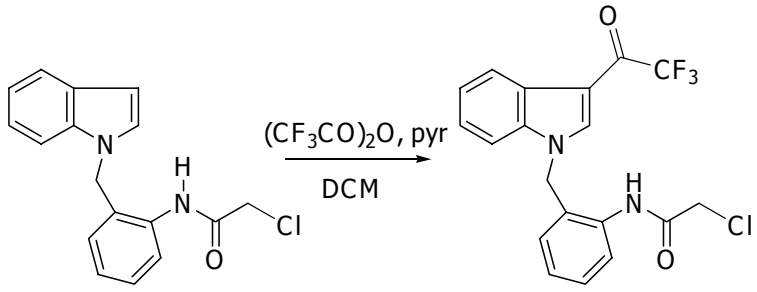
158 **170**

(i) K_2CO_3, DCM, $ClCH_2COCl$; (ii) NaH, THF, $ClCH_2COCl$

Scheme 2-20. Attempted synthesis of *N*-trifluoroacetylchloroacetamide 170.

An alternative approach to the preparation of compound **170** starting from the chloroacetamide **161** was then investigated (Scheme 2-21). Chloroacetamide **161** was

treated with sodium hydride followed by trifluoroacetic anhydride. While purification of the crude reaction mixture was attemped by preparative thin layer chromatography (PTLC) by dissolving it in a minimal volume of DCM, the solution formed a gel after leaving it for several minutes. The solution that remained was subjected to PTLC, and showed five UV-absorbing bands. Mass spectrometric analysis (CI^+) of the major band (lowest R_f) showed a parent ion at *m/z* 395 (MH^+), which confirmed that the $COCF_3$ group had been added to the molecule. However, the ^1H NMR spectrum revealed the presence of a broad singlet ascribed to the NH proton at 8.13 ppm together with a singlet ascribed to the indolic H-2 at 7.92 ppm. Also the expected indole C-3 (110.4 ppm) signal was absent in the DEPT spectrum. The ^{13}C NMR spectrum indicated the presence of a signal for the quaternary CF_3 group at 117.2 ppm (*J*= 285 Hz, ^{13}C-^{19}F). From the NMR analysis, the 3-trifluoroacetyl derivative **171** was proposed as the structure of the major product. This would result from electrophilic aromatic substitution at the activated indolic 3-position. Therefore, this attempted synthesis of *N*-trifluoroacetylchloroacetamide **170** was also unsucessful.

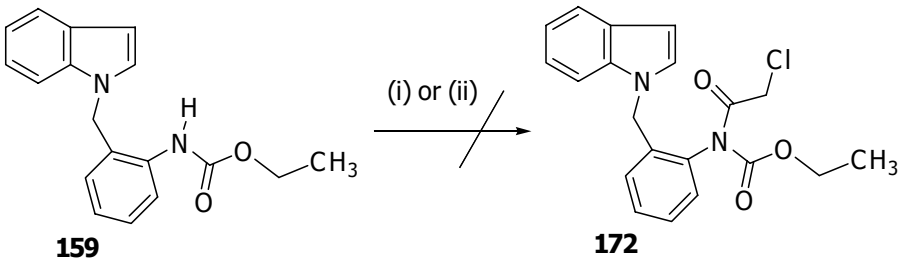


161 **171**

Scheme 2-21. Formation of *N*-{2-[1-(3-trifluoroacetyl)-1*H*-indolyl)methyl]phenyl}chloroacetamide 171.

Chloroacetylation of the carbamate **159** was unsuccessful using both potassium carbonate or sodium hydride as a base (Scheme 2-22). Using potassium carbonate, the starting material was recovered even after increasing the molar equivalents of potassium

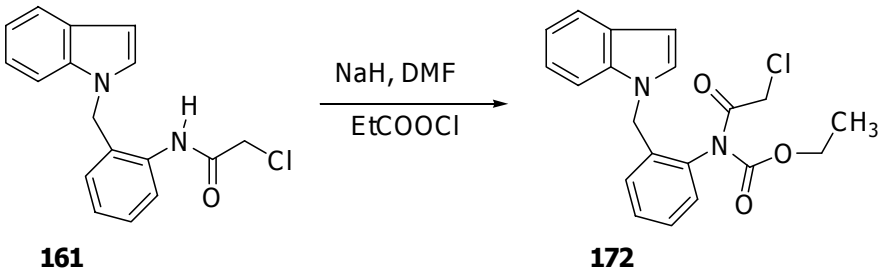
carbonate and chloroacetyl chloride. Use of a stronger base, such as sodium hydride, followed by addition of chloroacetyl chloride, failed to give **172** or show any addition of the chloroacetyl group at any position in the starting material. It appeared that the bulky steric properties of the carbamate could have obstructed the addition. Therefore, direct acylation was investigated starting with chloroacetamide **161** (Scheme 2-23).



Reagents: (i) K_2CO_3, $ClCH_2COCl$, DCM; (ii) NaH, $ClCH_2COCl$, THF

Scheme 2-22. Attempted synthesis of *N*-carbamoylchloroacetamide.

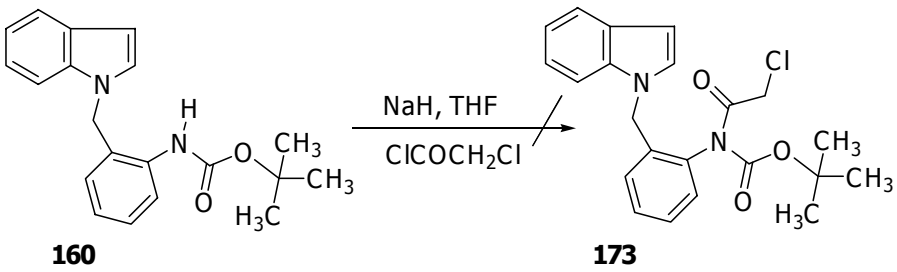
The chloroacetamide **161** was treated with sodium hydride in DMF and then ethyl chloroformate was added. After work up, the reaction mixture had changed colour from orange to yellow and then green. The mixture was purified using column chromatography to give compound **172** in 32% yield together with some starting material (10%). The changes in colour indicated other possible pathways taking place thus accounting for the low yield of the required product **172**.



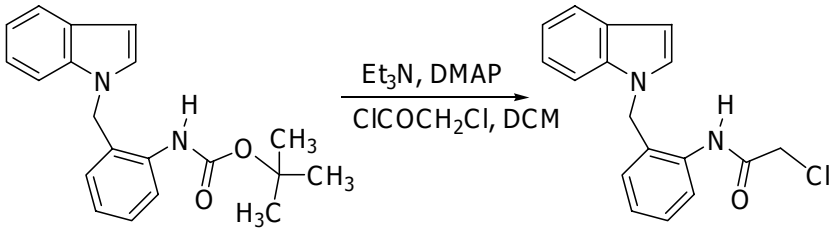
Scheme 2-23. Preparation of *N*-carbamoylchloroacetamide 172.

The HREI-MS of **172** gave a molecular ion at *m/z* 370.1094 consistent with the molecular formula $C_{20}H_{19}N_2O_3Cl$ and the addition of a carbamate group to the starting material. In the ^1H NMR spectrum of **172**, a signal for the methyl group was ascribed to a triplet at 1.09 ppm, and the methylene protons were observed as two sets of doublets at 3.92 ppm and 4.08 ppm. Likewise, in the ^{13}C NMR spectrum a signal for the methyl carbon was apparent at 14.3 ppm and for the methine carbon at 64.2 ppm.

Attempted synthesis of *N*-Boc-chloroacetamide **173** involved reaction of **160** with sodium hydride followed by chloroacetyl chloride (Scheme 2-24). After 16 hours, there was no evidence for successful acylation on the basis of ^1H NMR and MS analysis. Even when the *N*-Boc compound **160** was treated with triethylamine and a catalytic amount of DMAP followed by chloroacetyl chloride, there was no evidence for acylation, with mostly starting material being obtained and a small amount of the *N*-chloroacetamide **161** (Scheme 2-25).



Scheme 2-24. Attempted synthesis of *N*-Boc-chloroacetamide 173.



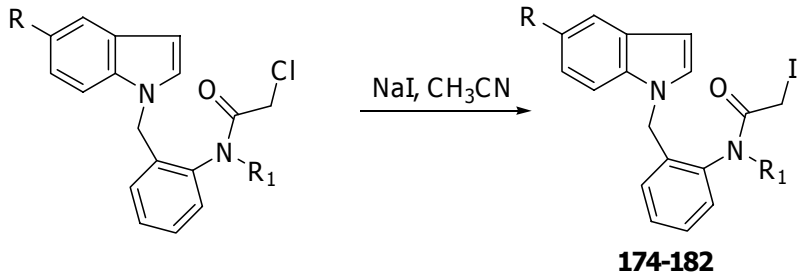
160 **161**

Scheme 2-25. Chloroacetylation of 160 in the presence of DMAP.

2.2.8 Preparation of iodoacetamides

Organoiodides are the most reactive precursors for atom transfer addition reactions and thus have been useful for radical addition reactions. A successful atom transfer reaction requires a suitably weak bond between carbon and the heteroatom allowing initiation to occur thermally in the presence of initiators such as AIBN or a photochemical initiator.[110] The bond dissociation energy (BDE) of a carbon-iodine bond is significantly lower than that of a carbon-chlorine bond (BDE: CH_3-I, 57 kcal/mol; CH_3-Cl, 83 kcal/mol).[87] Therefore, the use of an iodine atom as a leaving group usually results in the cyclised products, on the other hand the use of a chlorine atom frequently yields uncyclised reduction products.

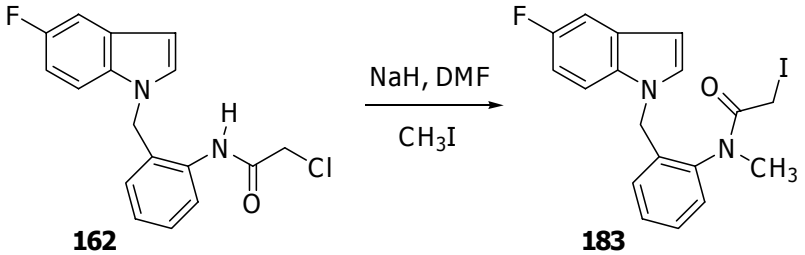
Based on the fact that the iodine is a better leaving group than chlorine, the iodoacetamides **176-184** were prepared as the precursors for the cyclisation step. Iodide exchange of the chloroacetamide was readily achieved using sodium iodide in acetonitrile[33] (Scheme 2-26). Table 2-3 shows the yields, MS and formulae for the iodoacetamides.



174-182

Scheme 2-26. General method for preparation of iodoacetamide.

The only exception was the formation of iodoacetamide **183** which was prepared by direct alkylation of the chloroacetamide **162** with methyl iodide in DMF after amide anion formation. The iodide anion, which is generated *in situ*, was then exchanged with the chlorine atom to afford the iodoacetamide in 66% yield (Scheme 2-27). The HREI-MS of this compound gave a molecular ion at m/z 423.0336, consistent with the molecular formula $C_{18}H_{17}N_2OIF$ and the addition of a methyl group and the replacement of the chlorine with an iodine.

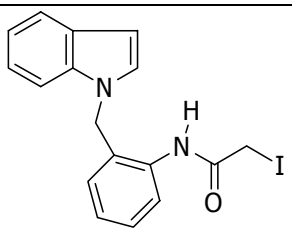
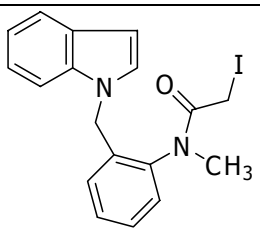
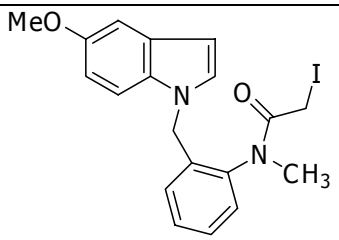
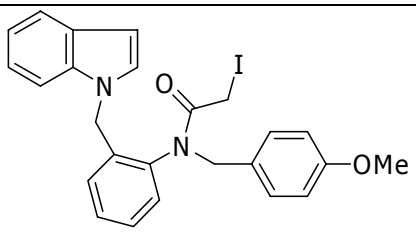
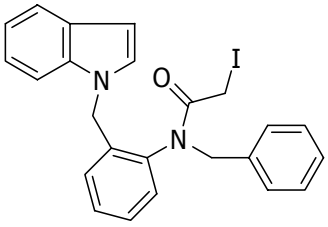


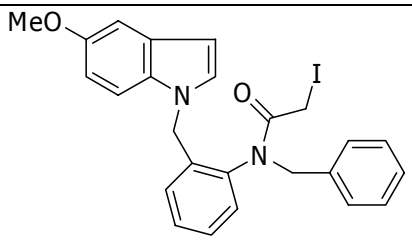
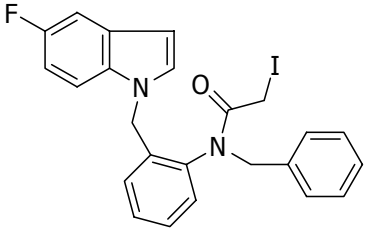
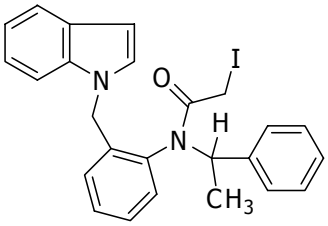
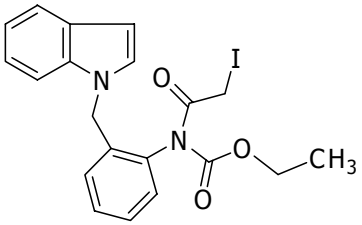
162 **183**

Scheme 2-27. Preparation of *N*-methyliodoacetamide by direct alkylation.

The ^1H NMR of the iodoacetamides in general showed that the two sets of doublets ascribed to the CH_2-I protons had moved upfield compared to the chloroacetamides and the ^{13}C NMR of the iodoacetamides showed the signal for the CH_2I carbon at between (-1) – (-3) ppm.[87] Otherwise, the ^1H and ^{13}C NMR spectra were similar to those of the precursor chloroacetamides.

Table 2-3. Results of the preparation of iodoacetamides.

Products		Yield (%)	HRMS	Formula
	**174**	87	390.0232 $[M]^+$	$C_{17}H_{15}N_2OI$
	**175**	93	404.0396 $[M]^+$	$C_{18}H_{17}N_2OI$
	**176**	70	434.0476 $[M]^+$	$C_{19}H_{19}N_2O_2I$
	**177**	70	510.0810 $[M]^+$	$C_{25}H_{23}N_2O_2I$
	**178**	96	480.0689 $[M]^+$	$C_{24}H_{21}N_2OI$

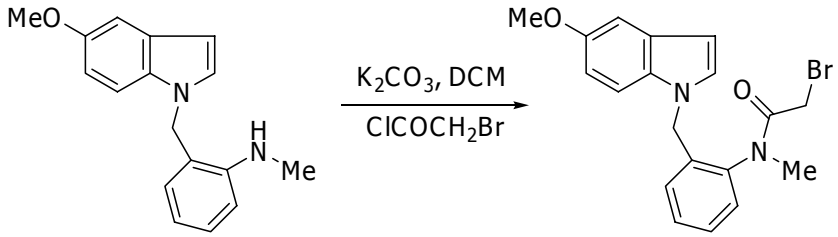
Product	Yield (%)	HRMS	Formula
 **179**	73	511.0868 $[MH]^+$	$C_{25}H_{24}N_2O_2I$
 **180**	89	498.0600 $[M]^+$	$C_{24}H_{20}N_2OI$
 **181**	82	495.0926 $[MH]^+$	$C_{25}H_{24}N_2OI$
 **182**	66	462.0445 $[M]^+$	$C_{20}H_{19}N_2O_3I$

2.2.9 Preparation of bromoacetamides

The bromoacetamides **184**-**185** were prepared using a similar approach to the preparation of the chloroacetamides, except bromoacetyl chloride was used as the acylating agent instead of chloroacetyl chloride.

Treatment of the *N*-methyl amine **150b** with bromoacetyl chloride in the presence of anhydrous potassium carbonate afforded the *N*-methylbromoacetamide **184** in 54% yield

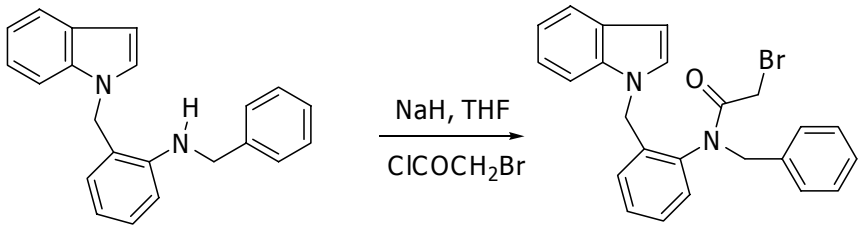
(Scheme 2-28). The product gave the expected M^+ ion at *m/z* 386.0624, consistent with the formula $C_{19}H_{19}N_2O_2Br$. The presence of the bromoacetyl group was evident from the ^1H NMR spectrum with a signal for the methylene protons ascribed to two sets of doublets at 3.53 ppm (*J*= 12.6 Hz) and 3.63 ppm (*J*= 12.6 Hz). Likewise, the ^{13}C NMR and DEPT spectra showed the methylene carbon signal at 41.2 ppm and the carbonyl carbon at 166.8 ppm.



150b **184**

Scheme 2-28. Preparation of *N*-methylbromoacetamide derivative.

Bromoacetylation of *N*-benzyl amine **153** was achieved in 68% yield by treatment of the amine with sodium hydride and bromoacetyl chloride (Scheme 2-29). The product was fully characterised by spectroscopic means. In the EI-MS, the product **185** gave the expected M^+ species at *m/z* 432.0851, supportive of the formula $C_{24}H_{21}N_2OBr$ and the addition of a bromoacetyl group to the starting material. The absence of the NH proton was apparent from the ^1H NMR spectrum. In addition, the presence of a doublet signal ascribed to the CH_2-Br protons was observed at 3.43 ppm. The bromoacetyl group was evident in the ^{13}C and DEPT spectra from the signals of the methylene carbon at 42.3 ppm and the quaternary carbonyl group at 166.8 ppm.



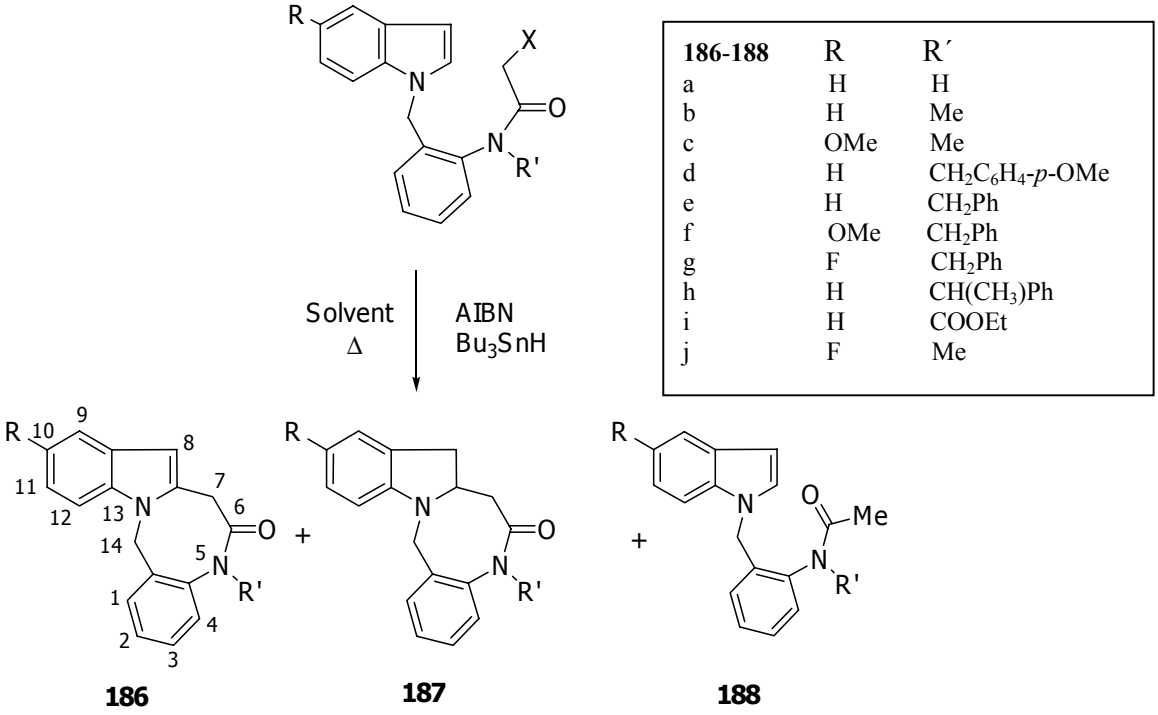
153 **185**

Scheme 2-29. Preparation of *N*-benzylbromoacetamide derivative.

2.2.10 Synthesis of benzodiazocinone derivatives using free radical cyclisation

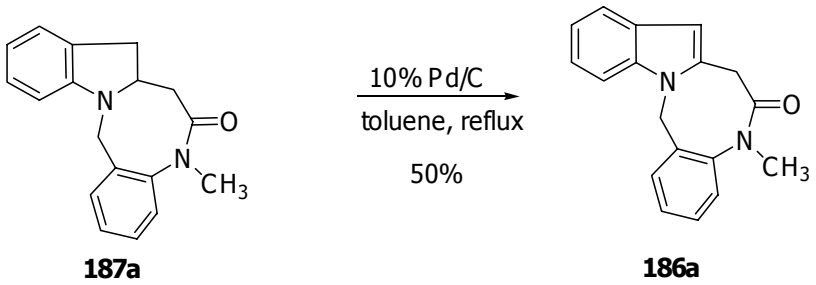
Free radical cyclisation reactions of the haloacetamides **161**, **163**, and **174-185** were induced by a slow addition of a 40 mM solution of tributyltin hydride (Bu_3SnH) (2.0 eq.) in the presence of azobisisobutyronitrile (AIBN) (1.0 eq.) in various solvents at reflux.

Slow addition of tributyltin hydride to a boiling toluene solution of the haloacetamides gave the indole fused eight-membered ring compounds **186-187** in fair yields, and also the simple reduced compound **188** (Scheme 2-30, Table 2-4). Dehydrogenation of **187a** was achieved in a separate aromatisation reaction with Pd/C in boiling toluene to give **186a** in 50% yield (Scheme 2-31).



186-188	R	R´
a	H	H
b	H	Me
c	OMe	Me
d	H	$CH_2C_6H_4$-*p*-OMe
e	H	CH_2Ph
f	OMe	CH_2Ph
g	F	CH_2Ph
h	H	$CH(CH_3)Ph$
i	H	COOEt
j	F	Me

Scheme 2-30. Free radical cyclisation reactions.



Scheme 2-31. Dehydrogenation reaction of 187a.

In the ^{1}H NMR spectra of compounds **186**, the H-8 proton appeared as a singlet signal at about δ 6.28-6.37, which was clearly separated from the other signals. In contrast, the signal attributed to the H-8 protons in compounds **187** appeared as a multiplet around δ 2.40-2.50 due to coupling with H-7a. In the ^{1}H NMR spectra of the acetamides **188**, a diagnostic singlet signal integrating for three protons ascribed to the acetyl group was apparent at around δ 1.80.

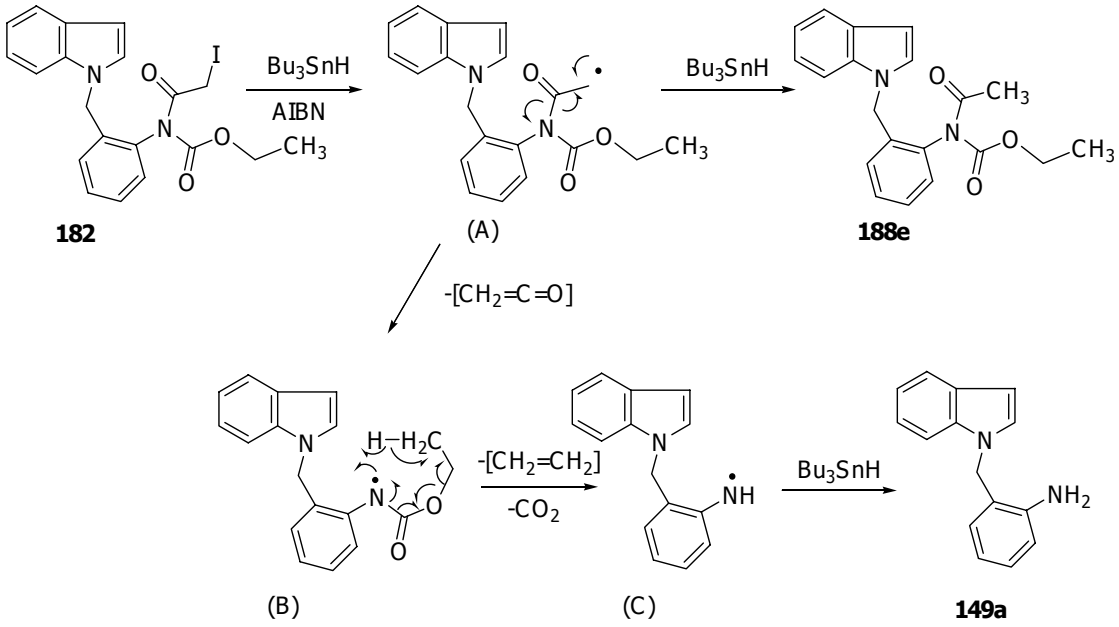
An increase in the cyclisation product yields was generally observed as the steric bulk of the protecting group on the haloacetamide nitrogen was increased.[93,111] When the unsubstituted haloacetamides (Entries 1 and 3, Table 2-4) were reacted, the products of simple reduction were also obtained. However, when a sufficiently large group (R′) was employed as a substituent on the amide nitrogen, the indole fused eight-membered ring cyclisation products were formed with the bromo or iodoacetamide precursors (eg. Entries 7 and 13, Table 2-4). In the case of the carbamate analogue **182** (Entry 10, Table 2-4), the simple reduced product was obtained together with the amine product **149a**.

Table 2-4. Radical cyclisation of haloacetamides using Bu_3SnH/AIBN in boiling toluene

Entry	Substate	R	R′	X	mmol	Yield (%)		
						186	**187**	**188**
1	**161**	H	H	Cl	0.16	-	-	82
2	**163**	H	Me	Cl	0.20	-	-	83
3	**174**	H	H	I	0.21	-	-	85
4	**175**	H	Me	I	0.13	20	60	20
5	**176**	OMe	Me	I	0.19	50	-	20
6	**177**	H	$CH_2C_2H_4$-*p*-OMe	I	0.33	13	11	7
7	**178**	H	CH_2Ph	I	0.08	25	43	10
8	**179**	OMe	CH_2Ph	I	0.12	25	-	<1
9	**181**	H	$CH(CH_3)Ph$	I	0.07	22	26[a]	
10	**182**[b]	H	COOEt	I	0.06	-	-	37
11	**183**	F	Me	I	0.14	35	-	17
12	**184**	OMe	Me	Br	0.12	24	-	33
13	**185**	H	CH_2Ph	Br	0.10	54	20[b]	

[a]mixture of **187** : **188** in a ratio of *ca* 1: 1 (determined by ^{1}H NMR); [b]mixture of **187** : **188** in a ratio of *ca* 2 : 1 (determined by ^{1}H NMR) [b] 34% yield of **149a** also obtained.

It is conceivable that in this particular case, that the intermediate radical (A, Scheme 2-32) could undergo a hydrogen abstraction from Bu_3SnH to afford a simple reduced amide **188e** or lose ketene to give an intermediate (B), which could then afford the radical (C) (with loss of ethylene and carbon dioxide) and finally **149a** after hydrogen abstraction from Bu_3SnH.

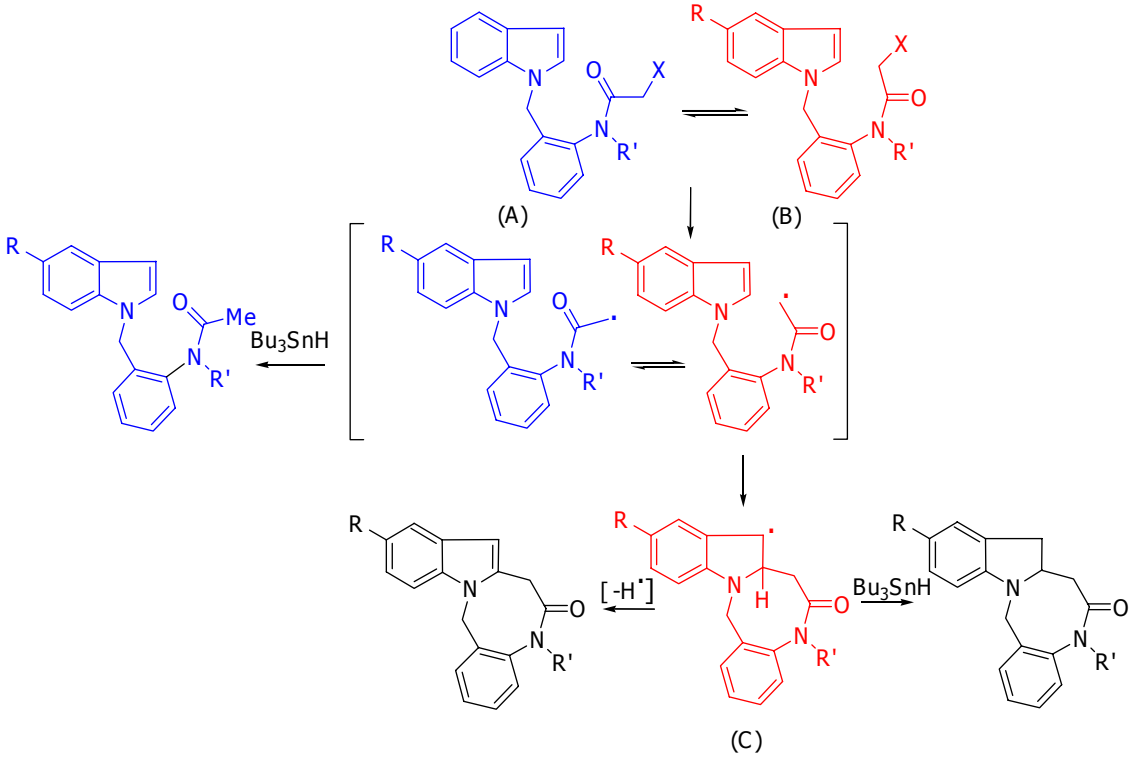


Scheme 2-32. Possible reaction of 182 with Bu_3SnH.

Ishibashi *et al*.[87] also observed halogen-dependent differences in radical cyclisation versus radical reduction with other *N*-benzylhaloacetamides. In their case, the chloroacetamide afforded cyclisation from the *cisoid* amide rotamer, while the iodoacetamide gave predominately the non-cyclised product from the favoured *transoid* rotamer. Clearly amide conformational preferences will be influenced by the nature of both the *N*-substituents and the nature of the haloacetamide.

The very bulky indolylmethyl substituent, together with the methyl or benzylic substitutent would induce a preference for the *cisoid* bromo and iodoacetamide rotamer (B)

(Scheme 2-33) which can cyclise to give the indole fused eight-membered ring precursor (C) after amide radical formation. On the other hand, the radical from the *transoid* rotamer (A) cannot cyclise but would give uncyclised reduction product instead.



Scheme 2-33. Proposed mechanism of radical cyclisation.

A temperature-dependence study of the cyclisation revealed increasing yields with higher boiling point solvents (Table 2-5).

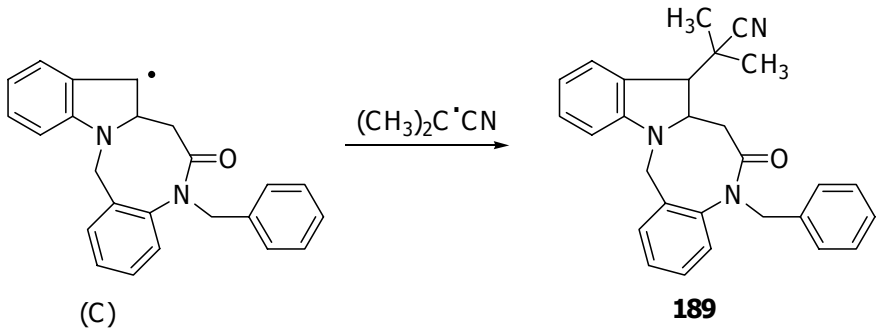
Table 2-5. Radical cyclisation of haloacetamides using Bu_3SnH/AIBN in various solvents.

Entry	Substrate	Solvent	Yield (%)		
			186	**187**	**188**
1	**175**	Mesitylene	44	-	-
2[a]	**178**	Toluene	25	43	10
3	**178**	Xylenes	57	-	-
4	**178**	Mesitylene	70	-	-
5	**178**	$(CH_3)_3CC_6H_5$	46	-	9
6	**179**	Mesitylene	29	-	-
7[a]	**179**	Toluene	25	-	<1
8	**180**	Mesitylene	23	-	15

[a] From Table 2-4

Cyclisations in high boiling point solvents eg. xylenes and mesitylene, increased the yields of **186** and neither the dihydroindole fused products **187** nor acetamides **188** were isolated when **175** or **178** was the substrate (Table 2-5). No products from radical attack on the aromatic hydrocarbon solvents were observed.[112] The increased yield of cyclisation products and the diminished formation of uncyclised reduction products in high boiling point aromatic solvents suggests that the amide rotamer (B) required for cyclisation after radical formation is increased in concentration in the equilibrium at higher temperatures relative to rotamer A.[87] Also, with radical attack on the heteroaromatic ring likely to be slow,[86] the increased temperature would be favourable for this reaction.

A 8-*exo-trig* addition of the amidylmethyl radical gives the indole radical (C) and then an oxidation step to give the product **186** (Scheme 2-33); the exact details of this latter step in other cyclisations has been the subject of much discussion, but it now seems likely that two possible pathways include hydrogen abstraction by the $(CH_3)_2C{\cdot}CN$ radical, plus reaction with AIBN.[113] In this connection, it is of interest to note that in a larger scale reaction involving **178**, some of the radical trapped adduct **189** was isolated.



Scheme 2-34. The radical trapped adduct 189.

Although Bu_3SnH has been used successfully in the formation of carbon-carbon bonds, either inter- or intramolecularly, several problems are associated with the use of this reagent including toxicity, instability to moisture and difficulty to remove the tin halide by-product from the desired products.[92] Alternative reagents have thus been investigated, including phosphites which contain a weak phosphorus-hydrogen bond, and can generate a phosphorus-centred radical on heating with AIBN.[92] Recently 1-ethylpiperidinium hypophosphite (EPHP) has been used for radical carbon-carbon bond formation.[114,115] Tris(trimethylsilyl)silane ($(TMS)_3SiH$) has also been used in radical reactions.[116] The Si-H bond strength (~350 $kJmol^{-1}$) is slightly stronger than the Sn-H bond (~ 310 $kJmol^{-1}$), which means that hydrogen atom abstraction from $(TMS)_3SiH$ is around 10 times slower

than from Bu_3SnH.[92] Unfortunately $(TMS)_3SiH$ is more expensive than Bu_3SnH and is also air-sensitive, requiring handling under argon.

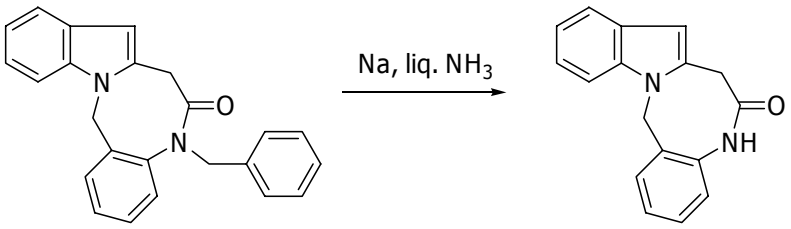
An investigation of the uses of EPHP and $(TMS)_3SiH$ as radical reagents in the intramolecular cyclisation of iodoacetamides was undertaken in this study and the results are reported in Table 2-6. Heating iodoacetamide **175** with EPHP (10 equiv.) and AIBN in benzene at reflux afforded the cyclised product **186b** (9%) and the simple reduced product **188b** (33%). The low yield of the cyclisation product is probably due to the lower reactivity of EPHP compared with tributyltin hydride (Entry 4, Table 2-4) and the low boiling point solvent (benzene) used. The same results were obtained when using $(TMS)_3SiH$ as the radical reagent. The yields of cyclisation products obtained were less than those from tributyltin hydride, and also more of the unwanted simple reduced products were obtained. Moreover, using a high boiling point solvent decreased the yield of cyclised product. This result, in contrast to the Bu_3SnH reaction, indicated that $(TMS)_3SiH$ might decompose at the higher temperature or it might react with the mesitylene.

Table 2-6. Results of the cyclisation reaction of iodoacetamides using EPHP and $(TMS)_3SiH$.

Entry	Substrate	Radical reagent	Solvent	Product (%)		
				186	**187**	**188**
1	**175**	EPHP	Benzene	9	-	33
2	**176**	$(TMS)_3SiH$	Toluene	10	-	36
3	**178**	$(TMS)_3SiH$	Toluene	31	-	54
4	**178**	$(TMS)_3SiH$	Xylenes	9	-	43

2.2.11 Debenzylation of *N*-benzyl substituted indolo[2,1-*d*][1,5] benzodiazocine-6-ones

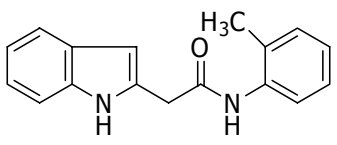
With a view to ultimately providing access to other *N*-substituted indolo[2,1-*d*][1,5]benzodiazocine-6-ones, a chemoselective means of removal of the *N*-benzyl group in **186e** was investigated. Deprotection of *N*-benzylamides is not straightforward and they can be difficult to cleave by typical catalytic hydrogenolysis.[117] Thus, harsher deprotecting methods, such as aqueous HBr and sodium in liquid ammonia have been used to remove the benzyl group. Debenzylation was achieved, using metallic sodium in liquid ammonia[118] to afford **29a** in 35% yield (Scheme 2-35). There was no unreacted **186e**, but some unidentified baseline material was observed in the PTLC of the reaction mixture.



186e **29a**

Scheme 2-35. Debenzylation using Na in liquid ammonia.

Selective addition of a solvated electron was expected at the less-electron rich aromatic ring of the benzyl protecting group. However, the reaction time was crucial to ensure a reasonable yield of the product. The most suitable time for the cleavage of the benzyl protecting group was 6 to 8 minutes. If the reaction mixure was left longer both the protecting group and the eight-membered ring were cleaved to give adduct **190**.



190

2.3 Attempted metal-mediated cyclisation

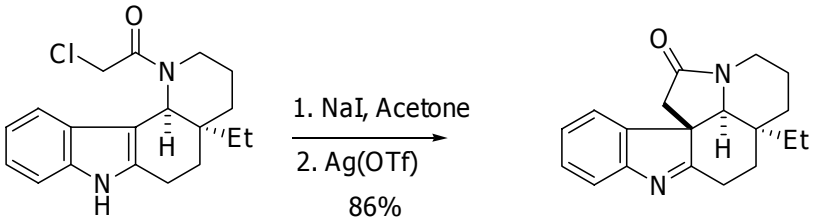
Metal-mediated reactions have gained increasing popularity in organic synthesis over the past decade[119] since the reagent Bu_3SnH (for radical generation) has toxicity problems and there are difficulties associated with complete removal of tin species from the reaction mixture.[92] Therefore, metal-mediated reations are of considerable interest as tools in cyclisation reactions.

2.3.1 Silver-mediated cyclisations

Silver salts have been used to induce intramolecular cyclisations in indole-based haloacetamides. Thus reaction of the α-bromoacetamide **191** with $AgBF_4$ resulted in cyclisation to the C-3 position of the indole ring (Scheme 2-36),[120] while the closure of the E ring was achieved in **193** by treatment of the haloacetamide with silver triflate[121] (Scheme 2-37). Thus we decided to investigate the cyclisation of iodoacetamide **178** to construct the indolodiazocinone **186**.

191 **192**

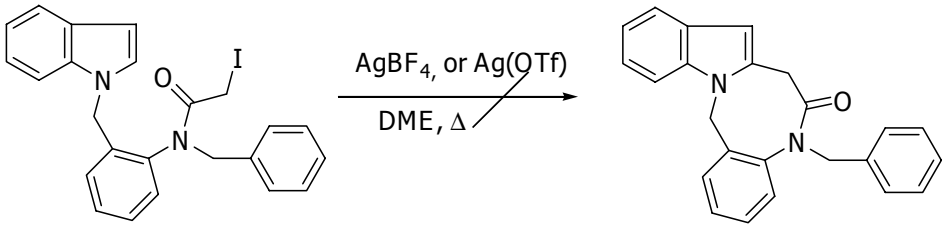
Scheme 2-36. Cyclisation of bromoacetamide 191 using $AgBF_4$.



193 **194**

Scheme 2-37. Cyclisation of chloroacetamide 193 using Ag(OTf).

Reaction of **178** with $AgBF_4$ in 1,2-dimethoxyethane at reflux[120] gave a variety of unidentified products, however no evidence for the cyclised product **186e** (Scheme 2-38) was observed from analytical TLC and LR-MS analysis. The failture to achieve silver-mediated cyclisation could be due to an unfavourable amide rotamer population at the temperature of the attempted cyclisations. When AgOTf was used in place of $AgBF_4$, the reaction mixture formed a gel after work up. No organic solvents could dissolve this gel and no cyclisation product could be indentified.



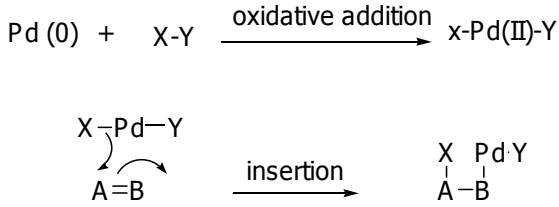
178 **186e**

Scheme 2-38. Attempted silver-mediated cyclisation.

2.3.2 Palladium-mediated cyclisation

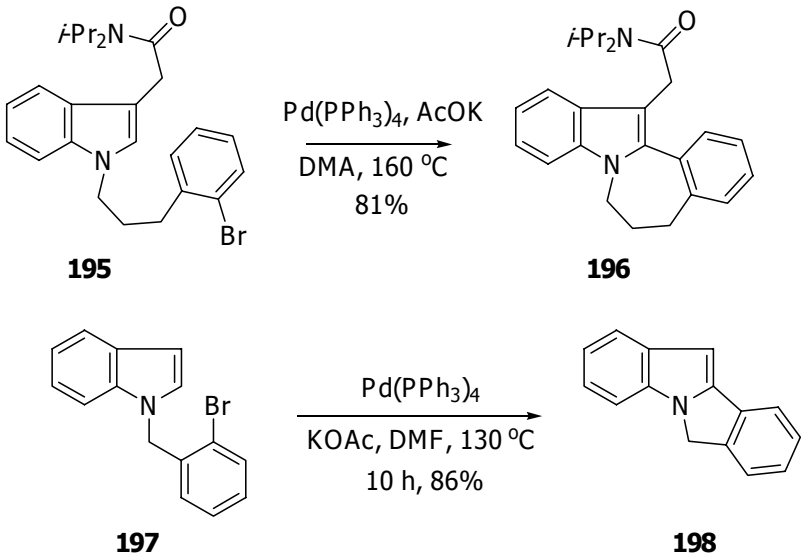
Palladium-mediated carbon-carbon bond formation has emerged as one of the most important methods in organic synthesis.[122] Oxidative addition of Pd(0) to alkenes, alkynes, and aryl halides forms the C-Pd bond which can then be inserted in adjacent double or

triple bonds (Scheme 2-39). Recently, many applications of this methodology have been used in the syntheses of various polycyclic frameworks via intramolecular cyclisations.



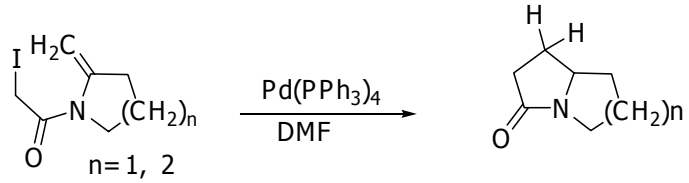
Scheme 2-39. General scheme for palladium-mediated carbon-carbon bond formation.

Intramolecular cyclisations via Pd coupling reactions mostly involve aryl halides. Oxidative addition of Pd to the aryl bromide is then followed by addition to double or triple bonds. For example, intramolecular arylation using $Pd(PPh_3)_4$ of indole derivatives **195** and **197** occurred at C-2 to give **196** when the C-3 position was substituted and **198** when C-3 was unsubstituted.



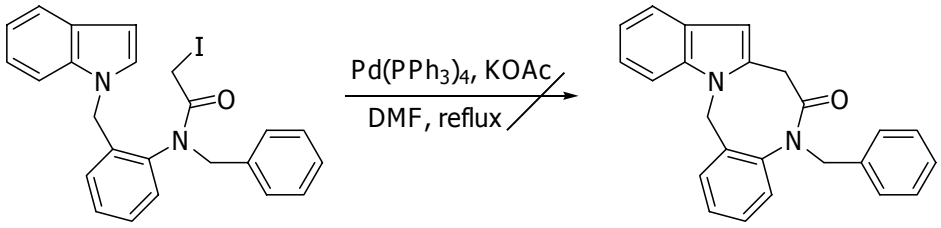
A study by Mori *et al.*[123] suggested that α-haloamides having an internal double bond could be cyclised to various five and six membered lactams in fair yields using $Pd(PPh_3)_4$. For example, cyclisation of iodoacetamide **199** with an equimolar amount of

$Pd(PPh_3)_4$ resulted in **200** in 37% yield; a σ-allylmetal complex is presumably involved as an intermediate.



199 **200**

However, cyclisation with the divalent palladium complex $Pd(OAc)_2$ or a catalytic amount of $Pd(OAc)_2$-PPh_3, was not successful.[123] Lactam **200** was obtained in 0% and 4% yield when using a catalytic amount of $Pd(OAc)_2$ and $Pd(OAc)_2$-PPh_3, respectively. As the results from **199**, cyclisations using $Pd(OAc)_2$ and $Pd(OAc)_2$-PPh_3 were not investigated, howver, in a current study, an attempt to cyclise the iodoacetamide **178** with $Pd(PPh_3)_4$ was also unsuccessful.



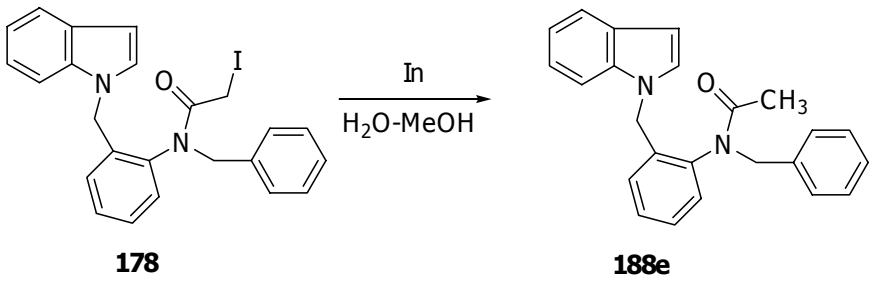
178 **186e**

Scheme 2-40. Attempted cyclisation using $Pd(PPh_3)_4$.

2.3.3 Indium-mediated cyclisation

Indium-mediated carbon-carbon bond formation in aqueous media has developed as a powerful method in organic synthesis. Since the first ionisation potential of indium (5.8 eV) is close to that of alkali metals such as sodium (5.1 eV), indium promotes SET (single electron transfer) processes with relative ease.[124] Therefore many useful indium-

mediated carbon-carbon bond formation reactions using indium as a single-electron-transfer radical initiator have been reported.[125-127] Naito *et al*.[125] reported that indium-mediated radical addition to an electron-deficient carbon-carbon double bond provided a convenient method for preparing new carbon-carbon bonds. On the basis of this, the radical addition to the indole ring using indium as a radical initiator was investigated in the current study. A mixture of **178** and indium (3.25 equiv.) was reacted in H_2O-MeOH at room temperature for 2 days. However, there was no evidence for any cyclised product being formed, only the simple reduced product **188** (3%), accompanied by the starting material (9%), and some unidentified baseline material were obtained. This was thought to be because of the slower reaction of indium-mediated cyclisation compared with the reduction. At the same time, the reaction did not go to completion, probably due to aggregation of the indium powder in the aqueous media, a phenomenon also observed by Naito *et al*.[126]



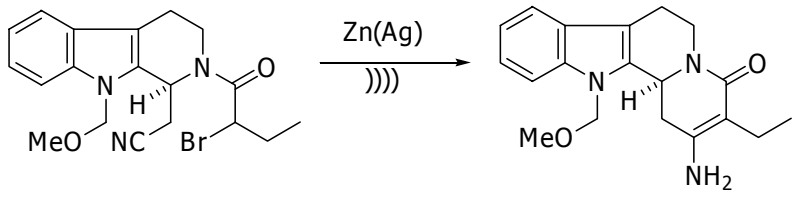
178 **188e**

Scheme 2-41. Reaction of iodoacetamide with In powder.

2.3.4 Zinc-silver couple mediated cyclisation

Zinc-silver couple has been used for various synthetic applications including the reduction of carbon-halogen bonds,[128] and the reduction of β-halo-α,β-unsaturated

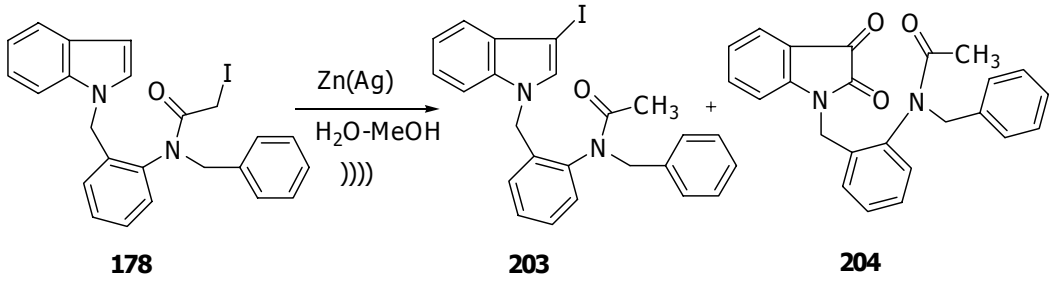
esters.[129] Furthermore, Meyers *et al*.[130] described the intramolecular cyclisation of a bromobutanamide **201** using zinc-silver couple. However, there have been no reports of Zn(Ag)-mediated cyclisation of haloacetamides on to an indolic 2,3-double bond.



201 **202**

To determine if this might be possible, the potential cyclisation of the iodoacetamide **178** using a zinc-silver couple was investigated. The zinc-silver couple was prepared as described by Taschner.[128] However, reaction of the zinc-silver couple with *N*-benzyliodoacetamide **178** in THF in a sealed tube at reflux with stirring for 5 hours, together with periodic sonication, did not give any cyclised products. Two products were obtained from this reaction, the major product being **203** which was obtained in 48% yield, and the minor product **204**, obtained in 35% yield (Scheme 2-42). Both structures were indentified on spectroscopic grounds. In the HREI-MS of **203**, the M^+ ion was present at *m/z* 480.0701, consistent with the formula $C_{24}H_{21}N_2OI$, which is the same formula as that for the starting material **178**. The ^1H NMR spectrum of **203** was different from the starting material however; the spectrum indicated the presence of an acetyl group from the new singlet signal at 1.83 ppm and the absence of the characteristic signal for the indole proton at C-3. The ^{13}C NMR spectrum of **203** also indicated the loss of the CH at the 3-position, with the presence of a new quaternary carbon signal at 56.8 ppm,[131] consistent with a 3-iodo substituent. Also the presence of the acetyl group was consistent with the carbonyl signal at 170.4 ppm, and the methyl signal at 22.5 ppm. The formation of **203** suggests

either iodine atom or iodonium ion formation in the reaction, with subsequent attack at the indolic 3-position.



Scheme 2-42. Reaction of iodoacetamide 178 with Zinc-Silver couple.

In the ^{1}H NMR spectrum of **204**, the characteristic signals for the indole protons at C-2 and C-3 were not present, which indicated that there were substituents in both of these positions. A doublet signal resonating at 6.15 ppm was ascribed to the indole H-7 proton. The ^{13}C NMR spectrum of **204** showed quaternary carbon signals at 158.4 and 183.6 ppm and which were ascribed to the carbonyl carbons at C-2 and C-3 of an indole-2,3-dione[132] respectively, together with a quaternary signal at 170.8 ppm ascribed to the amide carbonyl carbon. The HRCI-MS of this compound gave a peak at *m/z* 385.1615 (MH^{+}), consistent with the molecular formula $C_{24}H_{21}N_2O_3$. The formula supported the oxidation of the indole to afford the indole-2,3-dione derivative.[133]

2.4 Summary and Conclusions

It has been shown that, in contrast to photo-initiated reactions, an indole-fused eight-membered ring system can be accessed in fair yield by a thermal free radical cyclisation route from 1-substituted indole derivatives with appropriately positioned haloacetamide functionalities. The cyclisation depended on a favourable amide rotamer population prior to

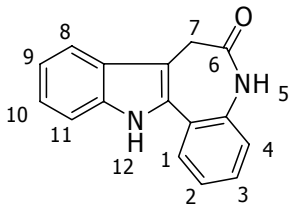
radical formation. The introduction of a sterically bulky protecting group on the haloacetamide nitrogen increased the concentration in the equilibrium of the required *cisoid* amide conformation for cyclisation. Cyclisations in high boiling point solvents such as xylenes and mesitylene also increased the yield of cyclised products. Selective deprotection of the benzyl protecting group was achieved in reasonable yield, providing potential access to other *N*-substituted indolo[2,1-*d*][1,5]benzodiazocine-6-ones.

Attempted metal-mediated cyclisations to form 8-membered ring fused indole derivatives were unsuccessful.

3 Indole seven membered ring heterocycles

3.1 Introduction

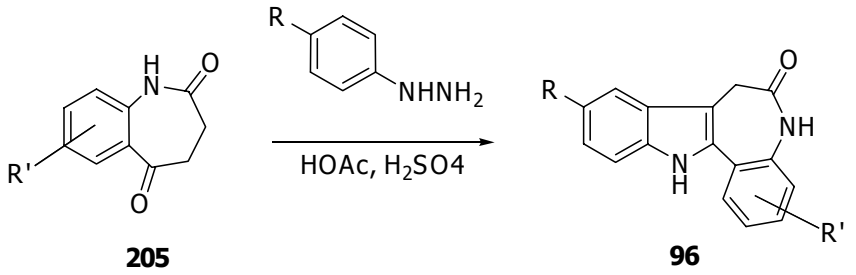
Among the indole fused seven membered ring heterocycles, the indolo[3,2-*d*][1]benzazepinone (paullone) systems have been of interest as a novel class which possesses potent cyclin dependent kinase (CDK)[134,135] and glycogen synthase kinase 3[136] inhibitory activity. CDK inhibitors are useful for treating diseases of cellular proliferation, abnormal protein phosphorylation and infectious diseases, such as cancer, atherosclerosis, Alzheimer's disease, and malaria.[137] Structure-CDK inhibitory activity relationships of paullone derivatives have been undertaken in order to discover the most potent analogues with antitumour activity. The most active paullone derivatives are kenpaullone and alsterpaullone (Figure 3-1). Alsterpaullone was reported[138] to be in preclinical development as a potential anti-tumour agent; kenpaullone is in clinical trials.[139]



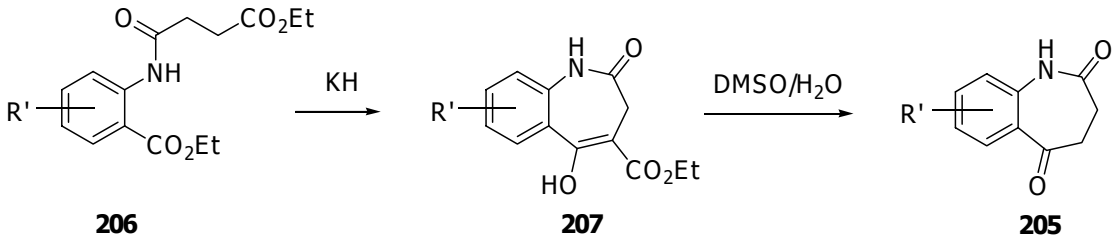
Name	Substitution	IC_{50} (μM)	Name	Substitution	IC_{50} (μM)
Alsterpaullone	9-NO_2	0.035	10-bromo-paullone	10-Br	1.3
Kenpaullone	9-Br	0.4	11-chloro-paullone	11-Cl	1.4
9-chloro-paullone	9-Cl	0.6	Paullone	None	7.0

Figure 3-1. General chemical structure and CDK1/cyclin B inhibition values for several paullones[135,140]

Previous approaches to the synthesis of the paullone system have been based on two strategies. The first strategy involves a preformed 7-membered ring and elaboration of the fused indole moiety by Fischer indolisation with phenylhydrazines. The second strategy relies on a 2,3-disubstituted indole precursor and completion of the 7-membered ring by N-C bond formation. Examples of the first paullone synthesis strategy include the preparation of the benzazepinediones **205** in a three step synthesis followed by Fischer indolisation with phenylhydrazines. Kunick *et al*[77] employed a Fischer indolisation of the 1*H*-[1]benzazepine-2,5(3*H*,4*H*)-diones **205** and phenylhydrazines in the synthesis of the substituted paullones **96**. The annulated azepinones **205** were obtained by dealkoxycarbonylation of the fused azepinecarboxylic esters **207**, which were prepared via a Dieckmann reaction with KH from diester **206**.[141]

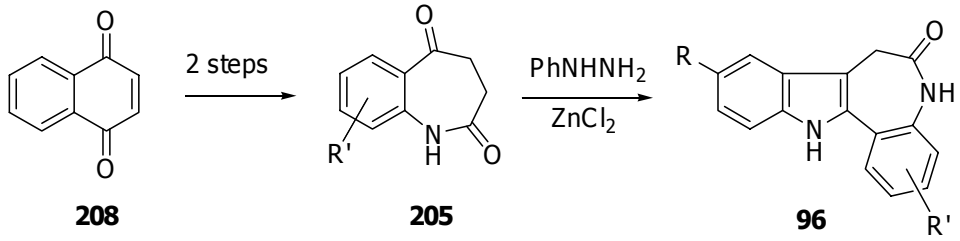


Scheme 3-1. Synthesis of the paullone system using Fischer indolisation.



Scheme 3-2. The synthesis of the key intermediate 1*H* -[1]benzazepine-2,5(3*H*,4*H*)-diones 205.

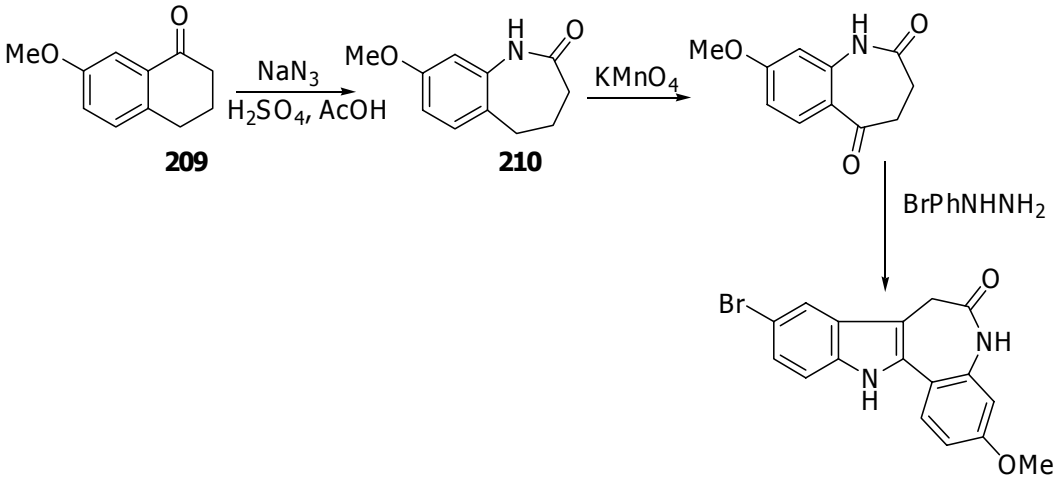
A synthesis of the parent paullone **96** (R= R´= H) has also been published by the Kozikowski group.[142] This method involved the Fischer indolisation of the α-keto lactam **205** giving the desired product in an overall yield of 75%. The α-keto lactam **205** (R´= H) was obtained by reaction of naphthoquinone **208** with sodium azide in sulphuric acid followed by catalytic hydrogenation.



208 **205** **96**

Scheme 3-3. The synthesis of paullone described by Kozikowski *et al.*[142]

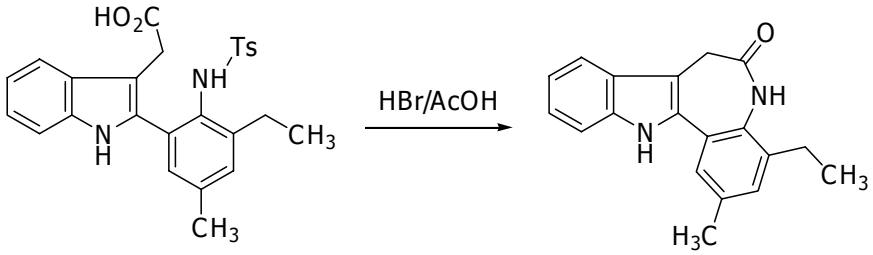
A similar method was described by Kunick *et al*.,[143] and began with the reaction of 7-methoxytetralone **209** with sodium azide and sulphuric acid in glacial acetic acid to give **210**, which was oxidised by $KMnO_4$ to the methoxy benzodiazepinedione. Fischer indole synthesis with 4-bromophenylhydrazine then furnished the substituted paullone (Scheme 3-4).



209 **210**

Scheme 3-4. The synthesis of paullone derivative described by Kunick *et al.*[143]

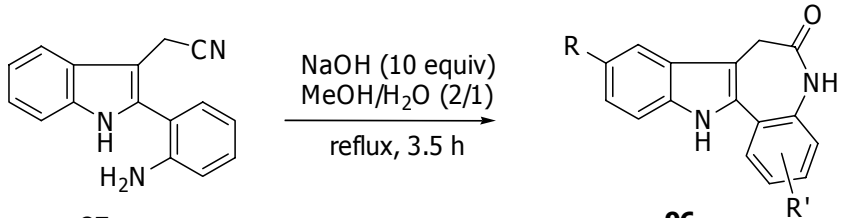
Examples of the second strategy involve the cyclisation of 2-arylindole precursors (Scheme 3-5). The key intermediate lactam **211** was obtained in eleven steps as an intermediate in a sequence directed towards the synthesis of iboga alkaloid selenium dehydrogenation products. Ring closure with HBr/AcOH initiated by cleavage of the tosyl group in the lactam precursor gave the paullone shown (Scheme 3-5).[144]



211

Scheme 3-5. Synthesis of a paullone via cyclisation of a 2-arylindole using HBr/AcOH.

As described in Chapter 1, Baudoin *et al.*[64] reported an alternative strategy using palladium-catalysed borylation/Suzuki coupling technology, under basic conditions, to obtain the intermediate **95**. Direct base-catalysed hydrolysis of **95** with alcoholic sodium hydroxide gave paullone **96** (R= R´= H) cleanly in 51% yield.



95 **96**

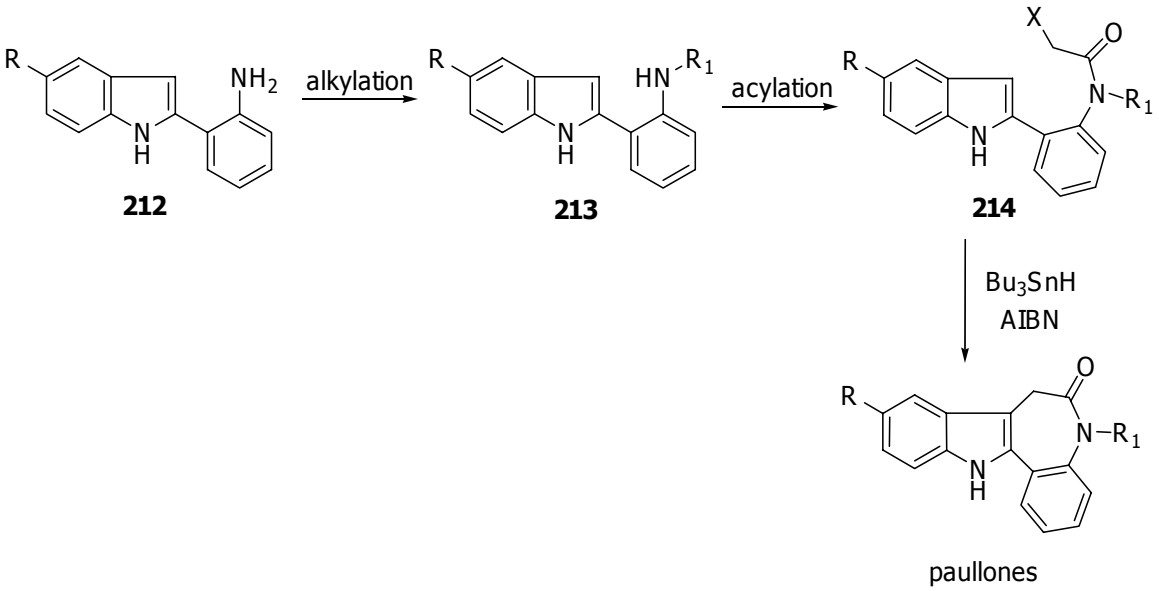
Scheme 3-6. Synthesis of the paullone via borylation/Suzuki coupling strategy. [64]

There are thus the two general synthetic methods for preparing paullones, one involving penultimate lactam formation to complete the 7-membered ring and the other involving indole elaboration from a pre-formed benzazepinedione. There has been no previous work done on using C-C bond formation in the last step to complete the 7-

membered ring. Intramolecular free radical cyclisation of an iodoacetamide was considered as a possible way to achieve this bond formation and the seven-membered ring fusion to the indole ring. This approach required the development of an efficient synthesis of the appropriate indole-fused iodoacetamide derivatives.

3.2 Proposed synthetic approach to indole fused seven membered rings

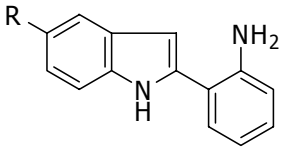
The synthetic approach to the desired indole fused seven-membered rings in the paullones involved intramolecular free radical cyclisation of a haloacetamide using the synthetic strategies described in Chapter 2 to afford the ring closure of the radical intermediate onto the indole ring. The proposed synthetic approach is shown in Scheme 3-7. Thus, monoalkylation of the 2-aminophenylindole **212** was expected to result in the formation of the secondary amine **213**, which could then be acylated to obtain the key precursor *N*-substituted haloacetamides **214** for the free radical cyclisation step.



212 213 214

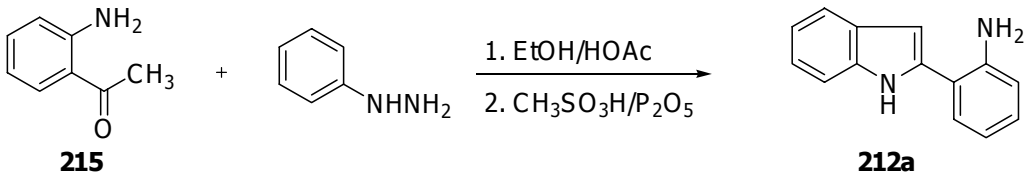
Scheme 3-7. Proposed new synthetic scheme to the paullones.

3.3 Preparation of 2-(2´-aminophenyl)indoles 212



212a R = H
212b R = OMe
212c R = F

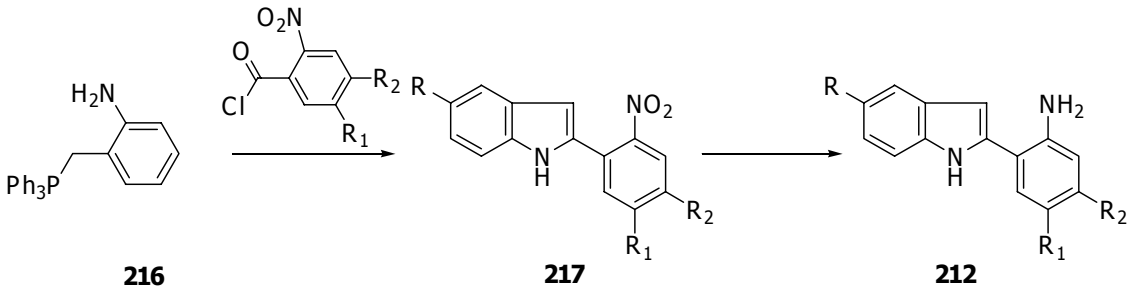
2-(2´-Aminophenyl)indole **212a** was commercially available and was obtained from Sigma-Aldrich Ltd. The other derivatives **212b-c** can be prepared via many methods. Most of the literature on the syntheses of compounds of type **212** involve the formation of indole rings. For example, Cava used the Fischer indole cyclisation of phenylhydrazone and aminoacetophenone **215** to form **212a** (Scheme 3-8) as an intermediate in the synthesis of the marine alkaloid hinckdetine A.[145]



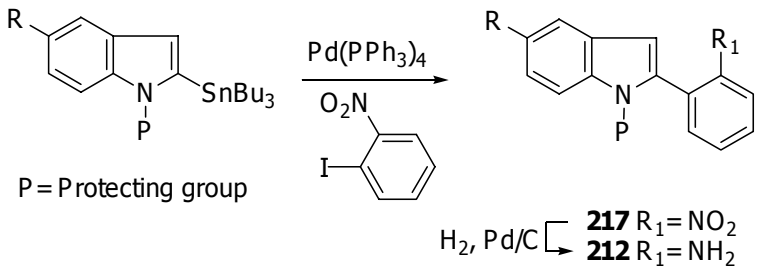
Scheme 3-8. Synthesis of 2-(2′-aminophenyl)indole using Fischer idolisation

Indole ring formation via the intramolecular Wittig reaction of 2-aminobenzyltriphenylphosphnium salts **216** and 2-nitrobenzoyl chlorides resulted in 2-(2′-nitrophenyl)indoles **217** which, after reduction with hydrogen and palladium on charcoal, resulted in the appropriately substituted 2-(2′-aminophenyl)indoles (Scheme 3-9).[146,147]

The preparation of 2-aryl substituted indoles can also be achieved by direct arylation of the pre-formed indole via lithiation at the C-2 position and then, after conversion to a stannane, a zinc or a boric acid derivative, can undergo palladium catalysed coupling with substituted benzene derivatives (Scheme 3-10).[148,149] An example of this strategy includes the palladium(0)-catalysed coupling of 2-tributylstanyl-*N*-protected indoles with 2-halonitrobenzene to give the 2-(*ortho*-nitrophenyl)indole **217**. Conversion of **217** via reduction gave the desired 2-(2′-aminophenyl)indole **212**.[150]

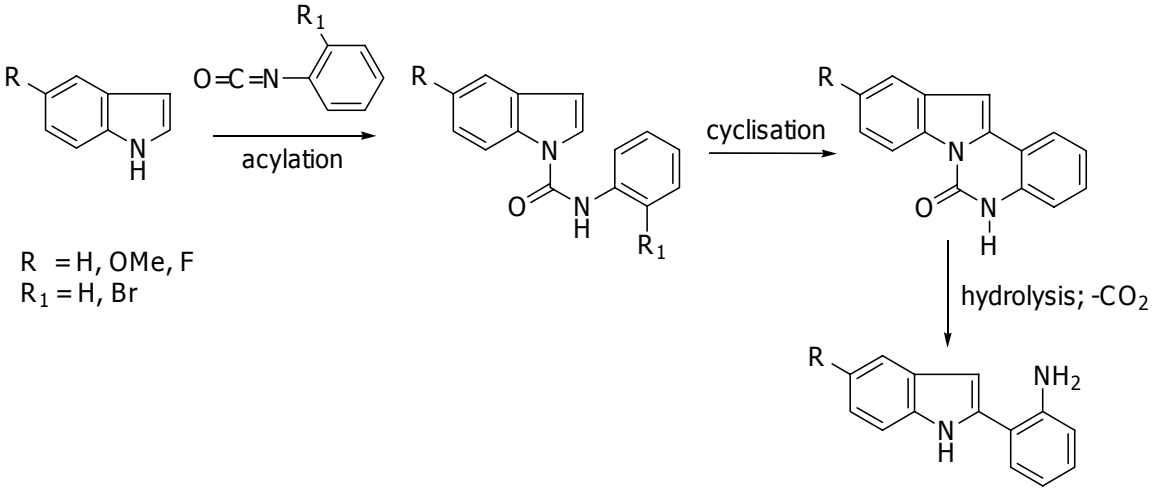


Scheme 3-9. Preparation of 2-aryl substituted indoles via intramolecular Wittig reaction.



Scheme 3-10. Direct C-2 arylation reaction.

In the current study, an alternative new approach to obtain substituted 2-(2´-aminophenyl)indoles from pre-formed indoles was developed through *N*-acylation of 5-substituted-1*H*-indole, followed by palladium-induced cyclisation, hydrolysis of the urea and subsequent decarboxylation, as proposed in Scheme 3-11.

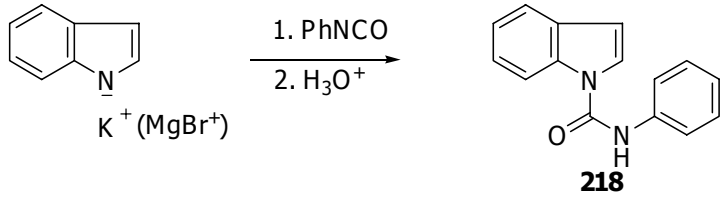


Scheme 3-11. General scheme for the preparation of 2-(2´-aminophenyl)indoles

3.3.1 Acylation of 1*H*-indoles with isocyanates

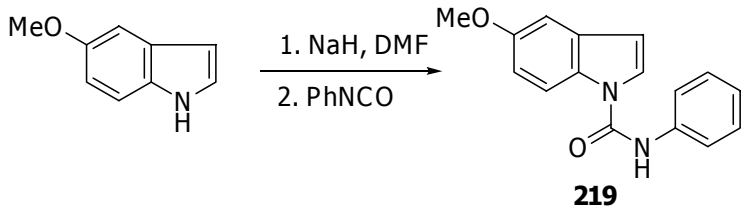
As established by Papadopoulos and Bedrosian,[151] acylation of indolylpotassium or indolylmagnesium bromide with phenyl isocyanate in THF gave only 1-indolecarboxanilides **218** in 56% yield, with no acylation being observated at the C-3

position (from the charge delocalisation of the anion). Some adaptions were made to this reaction in the current work.



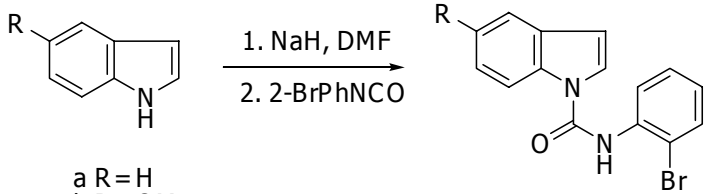
Scheme 3-12. Preparation of 1-indolecarboxanilides 218.

The change of reaction conditions to a sodium salt in DMF is far more favourable for reaction on nitrogen as it promotes greater ionic character of the deprotonated indole. Therefore, treatment of 5-methoxy-1*H*-indole using sodium hydride provided the initial deprotonation of the indolic NH. Nucleophilic attack by phenyl isocyanate in DMF yielded only the 1-indolecarboxanilide **219** in 95% yield.



In the CIMS, the product **219** gave an ion for the expected MH^+ species at *m/z* 267.1124, consistent with the formula $C_{16}H_{15}N_2O_2$. The presence of extra aromatic protons was apparent from the ^1H NMR spectrum. The signal ascribed to the urea NH was observed at 7.32 ppm. A signal attributable to the H-7 proton was observed further downfield than for the respective signal in the starting material at 8.02 ppm. This can be explained by the deshielding effect of the urea carbonyl oxygen. Evidence for the urea carbonyl carbon was observed in the ^{13}C NMR spectrum with a signal resonating at 156.1 ppm.

Acylation of 1*H*-indoles using the same conditions with 2-bromophenyl isocyanate resulted in a drop in the yields of **220a-c** to 43-56%. The lower yield may have been due to the bulk of the *o*-bromo substituent in the isocyanate hindering nucleophilic addition. The products were identified by their ascribed characteristic urea signals observed in both the ^{1}H-NMR and ^{13}C NMR spectra as well as via LRMS and HRMS.



a R = H
b R = OMe
c R = F

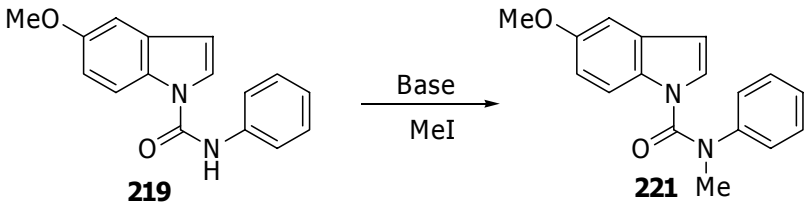
220a 43%
220b 56%
220c 53%

The ^{1}H NMR spectrum of **220a** revealed four extra aromatic protons which were not present in the ^{1}H NMR of the starting material as well as a broad signal ascribed to the urea NH resonating at 8.00 ppm. A downfield shift of the doublet signal at 8.25 ppm representative of the H-7 proton indicated that acylation had occurred at the indole nitrogen. The corresponding urea carbonyl carbon was also observed in the ^{13}C NMR spectrum at 148.9 ppm. This data suggested successful acylation of the NH indole had occurred and there was further confirmation of this from the HRCI-MS, which showed a peak for the MH^{+} ion at *m/z* 315.0091, consistent with the formula $C_{15}H_{12}N_2O^{79}Br$.

The ^{1}H NMR and ^{13}C NMR spectra of **220b** and **220c** also showed the characteristic signals for the urea groups similar to that of **220a**. The structures were also confirmed by HRCI-MS with MH^{+} ions at *m/z* 347.0204 and 335.0006 which correlate with the molecular weights and molecular formulae of the desired products **220b** and **220c**, respectively.

3.3.2 *N*-alkylation reactions of ureas

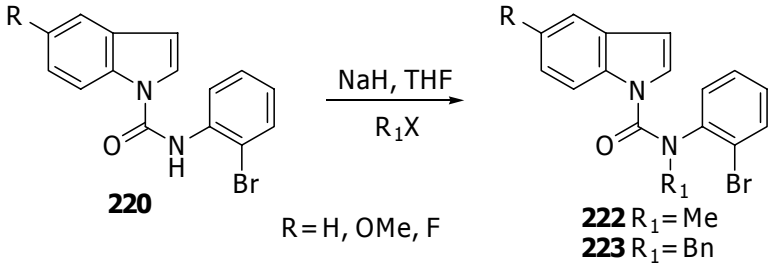
The urea **219** was alkylated to its *N*-methyl derivative using the method described in Thal *et al*.[120] Reaction of **219** with potassium hydroxide and methyl iodide in DMSO gave the methylated product **221** in 43% yield. This reaction was optimised by using sodium hydride in THF for deprotonation of the urea, which improved the yield of **221** to 76%. The improved yield might be due to the need for a stronger base to deprotonate the urea NH. Moreover, potassium hydroxide is generally known to hydrolyse ureas.



219 **221**

Scheme 3-13. General synthetic route for alkylation of urea.

Alkylations of **220a-c** using sodium hydride in THF with methyl iodide or benzyl bromide yielded the urea derivatives **222** and **223**. The resulting yields are shown in Table 3-1.



220

222 R_1 = Me
223 R_1 = Bn

The ^{1}H NMR spectra of **221** and **222** revealed the absence of the amide NH proton and contained a singlet signal in the range of 3.40-350 ppm, which was indicative of the methyl protons. The ^{13}C NMR spectra showed a resonance at about 39.0 ppm ascribed to the methyl carbon, while the ^{1}H NMR spectrum of **223** showed two broad singlets in the

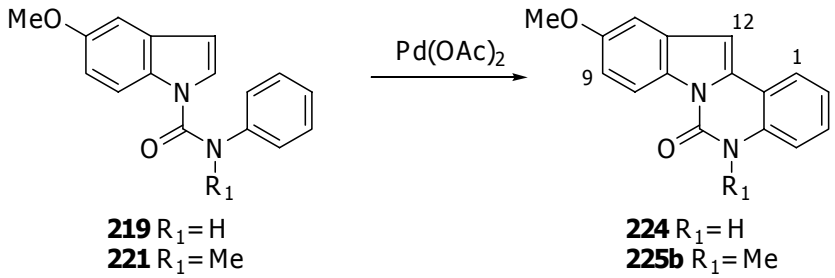
range of 4.60-5.40 ppm, representative of the benzylic protons and the five extra aromatic protons which were not present in the starting material. The broadening phenomenon of the benzylic protons may be explained by steric hindrance of rotation about the benzyl group and the *o*-bromophenyl urea moiety. The ^{13}C NMR spectra showed a resonance in the region of 54.0 ppm ascribed to the benzylic carbons.

Table 3-1. *N*-alkylation of ureas 220a-c

220	Yield (%)	
	222	**223**
a (R= H)	76	62
b (R= OMe)	88	81
c (R= F)	70	91

3.3.3 Palladium cyclisation of ureas

An initial attempt using palladium-induced oxidative cyclisation of **219** followed the method described by Itahara.[152] The method involved carbopalladation using Pd (II) species in glacial acetic acid at reflux for 8 hours. However work up and purification of the reaction did not result in the desired cyclised product **224** (R= OMe) (Scheme 3-14).



219 R_1 = H
221 R_1 = Me

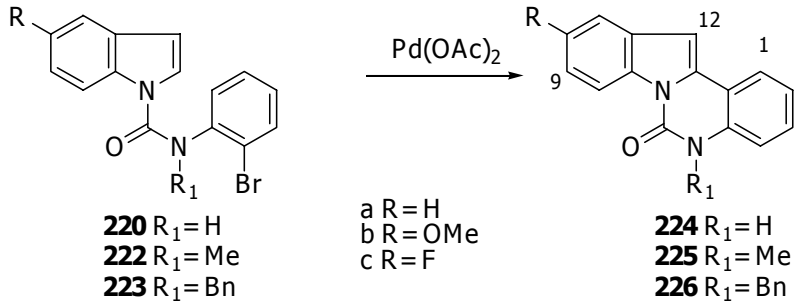
224 R_1 = H
225b R_1 = Me

Scheme 3-14. General precedure for oxidative palladium coupling cyclisation

The cyclisation reaction was re-attempted using the *N*-methyl derivative of **219**, compound **221**. After reaction under the same conditions as previously mentioned, analytical TLC showed only starting material. The reaction was continued at reflux for a further 2 days and after this time TLC analysis showed a new band at almost the same R_f as the starting material. The crude product was purified by flash column chromatography yielding the cyclised product **225b** in 20% yield as a white solid together with the starting material (9%) (Scheme 3-14). Evidence for the cyclised product was apparent from NMR spectroscopy and mass spectral analysis. The ^{1}H NMR spectrum of **225b** showed the presence of a singlet signal integrating for one proton at 6.99 ppm indicative of H-12. This signal appreared as a doublet in the starting material **221**. The DEPT spectrum comfirmed the loss of the C-2 and C-2′ (or C-6′) methine carbons. The apprearance of two more signals assigned to quaternary carbons in the ^{13}C NMR spectrum was consistent with oxidation cyclisation to the desired indolic C-2 position. The HRCI-MS displayed a peak at *m/z* 279.1122 (MH^+), consistent with the molecular formula $C_{17}H_{15}N_2O_2$ of the desired cyclised product.

The low yield of the cyclised product was probably due to an unfavourable conformation of the urea group for cyclisation. Thus an optimisation was attempted using propanoic acid as a higher temperature solvent to induce the molecule into the required conformation. However, mainly starting material (33%) was obtained in this reaction. Although two new bands at higher R_f values than that of the starting material **221** were observed, the separation using PTLC with multiple development failed to give any products. The unsucessful cyclisation using propanoic acid compared to acetic acid may be because propanoic acid might not be as good a solvent as acetic acid to protonate the acetate ligand. This protonation makes the Pd(II) species more electrophilic thus increasing

the rate of electrophilic palladation of the indole ring.[153] As this reaction was time consuming and low yielding, a change to another palladium catalysed cyclisation based on the Heck reaction[120] was attempted in the current work.



Scheme 3-15. Cyclisation via a Heck coupling reaction.

The initial cyclisation using a Heck coupling reaction was attempted with **220a**. Reaction with a catalytic amount of $Pd(OAc)_2$ with triphenylphosphine as a ligand and potassium carbonate as a base in DMF under refluxing conditions showed none of the starting material present after heating at reflux for 3 hours; the crude reaction mixture showed no trace of the expected cyclised product **224a** on the basis of CI-MS analysis.

Using the same conditions as noted above, the *N*-alkylated ureas **222** and **223** were then reacted. After work up of these reactions, analytical TLC clearly showed only one band in each reaction which had a very similar R_f to that of the starting material. Observation of these bands under a UV lamp did not indicate any difference, however, after staining the TLC plate with I_2 vapour, a colour difference between the starting materials and the corresponding products was observed. The results are shown in Table 3-2. NMR spectroscopy and mass spectrometric analysis were used to identify these compounds. The absence of the bromine atom and the indolic H-2 proton of the starting material were noted as well as a singlet signal ascribed to the H-12 proton, which in the gHMBC spectrum

showed a correlation to the carbonyl carbon. The HREI-MS of each product also confirmed the loss of the bromine atom and gave molecular formulae consistent with the corresponding cyclised products.

Thus, the Heck coupling reactions gave clean cyclisation products from the *N*-(2-bromophenyl)-*N*-alkyl-1-carboxamides in good yields.

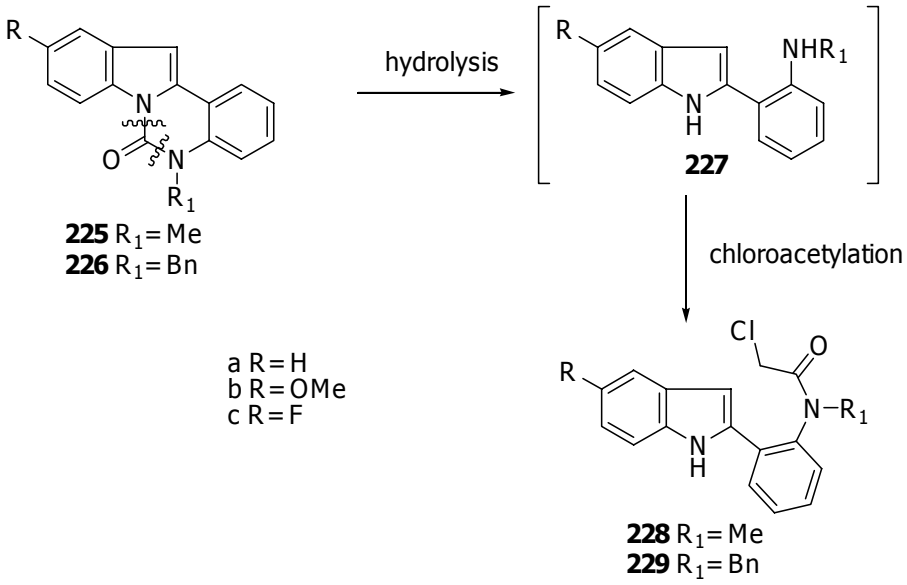
Table 3-2. The Heck coupling reaction of *N*-(2-bromophenyl)-*N*-alkyl-1-carboxamides

Starting material **222**	Product (%) **225**
a (R= H)	87
b (R= OMe)	55
c (R= F)	76

Starting material **223**	Product (%) **226**
a (R= H)	66
b (R= OMe)	88
c (R= F)	69

3.4 Preparation of chloroacetamides

Preparation of the chloroacetamides from the cyclised products required a two step synthesis; firstly a hydrolytic ring opening to give the 2-(2′-aminophenyl)indole derivative **227** was necessary followed by acetylation with chloroacetyl chloride to afford the desired chloroacetamide intermediates **228** and **229** (Scheme 3-16).



Scheme 3-16. General scheme for preparation of the chloroacetamides.

3.4.1 Hydrolytic ring opening of the cyclised products

Hydrolysis of ureas and subsequent decarboxylation can be achieved with hot concentrated sodium hydroxide solutions.[154] Thus urea **225a** was heated under reflux with 25% NaOH in EtOH for 24 hours to afford the ring opened product *N*-methyl-2-(2′-aminophenyl)indole **227** (R= H, R_1= Me) in quantitative yield (Scheme 3-16). The EI-MS of **227** (R= H, R_1= Me) gave an ion at *m/z* 222, consistent with the loss of a carbonyl group from the starting material. The ^{1}H NMR spectrum of **227** (R= H, R_1= Me) showed the presence of two broadened singlets which were ascribed to the indole NH proton and the amine NH proton at 8.30 ppm and 5.10 ppm, respectively. This indicated cleavage of the two CO-N bonds in the urea had occurred. However, **227** changed colour from yellow to blue after coming in contact with air, and thus is was chloroacetylated directly.

3.4.2 Chloroacetylation

Due to the instability of *N*-methyl-2-(2′-aminophenyl)indole **227** (R= H, R_1= Me), acylation without further purification was conducted using chloroacetyl chloride and K_2CO_3 in THF to give the chloroacetamide **228a** in 70% yield.

Formation of chloroacetamide **228a** was confirmed by the presence of signals at 3.81 ppm and 3.87 ppm in the ^{1}H NMR spectrum and by the apprearance in the ^{13}C NMR spectrum of a signal at 41.9 ppm supportive of the acetamide functionality. The absence of a signal corresponding to the amine NH proton (at 5.10 ppm) indicated acylation had sucessfully occurred at this amine nitrogen. The HRCI-MS of **228a** displayed a peak at *m/z* 299.0945 (MH^+), consistent with the molecular formula $C_{17}H_{16}N_2O_2Cl$.

Analytical TLC of the reaction mixture during hydrolytic ring opening of the ureas **225b** and **225c** using the aforementioned method showed no starting material **225c** remained after 24 hours. However, about 50% of the starting material remained in the hydrolysis of **225b** after the same time. The reaction was continued for a further 48 hours, however, the reaction mixture still showed a small amount of starting material **225b** remaining (determination by TLC analysis) and a new compound which had a similar R_f but a different colour when stained with I_2 vapour compared to that from **225b**. Extended reaction at reflux for longer than 48 hours resulted in the break down of both starting material and product. The harsh reaction conditions needed for the hydrolysis of the 5-methoxy urea derivative **225b** may be due to the electron donating properties of the methoxy group affecting the susceptibility of the urea carbonyl group to nucleophilic attack by the hydroxide ion. The fluoro derivative **225c** with the electron withdrawing fluoro

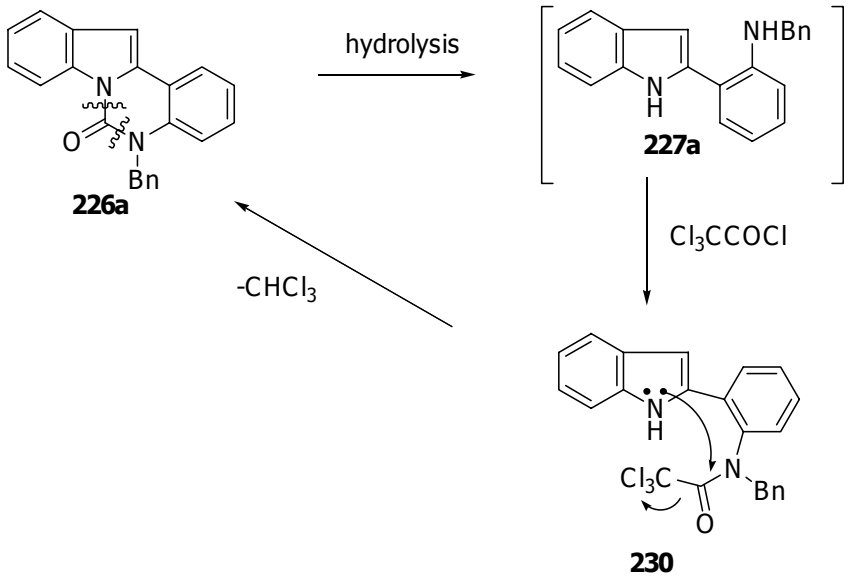
group would make the carbonyl group more susceptible to such attack, and hence this reaction proceeded more rapidly.

Chloroacetylation of the crude products from both reactions with chloroacetyl chloride gave **228b** and **228c** in 64% and 79% yield, respectively after purification. The HR-MS of **228b** and **228c** were supportive of the molecular formulae which would be expected for the required chloroacetamide products. The ^{1}H NMR and ^{13}C NMR spectra of both compounds showed the characteristic signals for the haloamide groups.

Similar results were obtained when the ureas **226a-c** were hydrolysed with sodium hydroxide. After 24 hours, no urea starting materials were observed in the reactions of **226a** and **226c** which were then worked up, but reaction of **226b** was allowed to continue at reflux for a further 24 hours. Acylation of **227a**, **227b** and **227c** with chloroacetyl chloride afforded chloroacetamides **229a**, **229b** and **229c** in 79%, 71% and 82% yield, respectively. The structures were identified by NMR spectroscopy and mass spectrometric analysis. In the ^{1}H NMR spectra of **229a-c**, the methylene protons of the chloroacetyl groups were ascribed to two doublet signals at 3.70-3.77 ppm and 3.82-3.88 ppm. The indolic NH protons were observed at 7.86 ppm for **229a**, 8.17 ppm for **229b** and 7.77 ppm for **229c**. The chloroacetyl groups were evident in the ^{13}C NMR spectra by signals for the methylene carbons at 42.4 ppm for **229a**, 42.3 ppm for **229b** and 42.5 ppm for **229c**. The HREI-MS of all compounds were matched with the required molecular formulae of these products.

Acylation of **227a** with trichloroacetyl chloride yielded the desired trichloroacetamide in 21% yield and the urea **226a** in 17% yield. The low yield of the trichloroacetamide **230** was probably be due to the moisture sensitivity of trichloroacetyl chloride and the bulk of the trichloromethyl group which would hinder acylation.

Moreover, the trichloroacetyl group is a good leaving group, therefore, nucleophilic attack by the indolic nitrogen on the carbonyl carbon could result in cyclisation back to the urea starting material **226a** (Scheme 3-17).

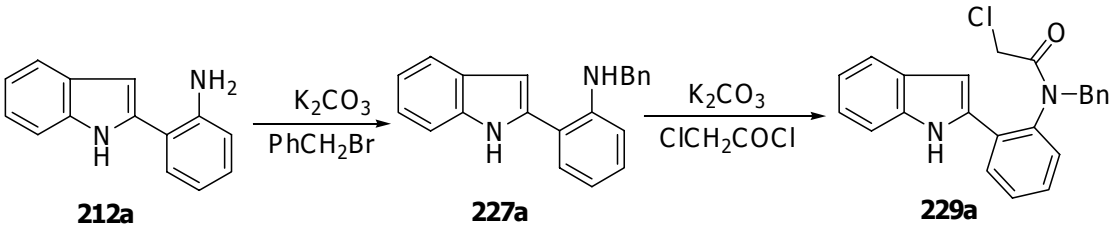


Scheme 3-17. Mechanism for the ring cyclisation of 230.

In the ^{1}H NMR spectrum of **230**, the benzylic protons were ascribed to two broad signals at 3.95 ppm and 5.70 ppm. This is due to a slow interconversion of the bulky trichloroacetamide rotamers. The absence of the amine NH proton also verified the addition of the trichloroacetyl group to the 2-(*N*-benzylaminophenyl)-1*H*-indole. In the ^{13}C NMR spectrum of **230**, a signal assigned to the CCl_3 carbon was observed at 103.0 ppm and a signal assigned to the carbonyl carbon was observed at 160.9 ppm. The HREI-MS gave a molecular ion at *m/z* 442.0405 consistent with the molecular formula $C_{23}H_{17}N_2O^{35}Cl_3$.

A separate reaction for prepration of the chloroacetamide **229a** was attempted by chloroacetylation of **227a**, which was prepared in turn in 45% yield by the direct

benzylation of commercially available 2-(2′-aminopheyl)-1*H*-indole **212a** (Scheme 3-18). The chloroacetamide **229a** was obtained in 79% yield after purification.



Scheme 3-18. Preparation of chloroacetamide 229a from the amine 212a.

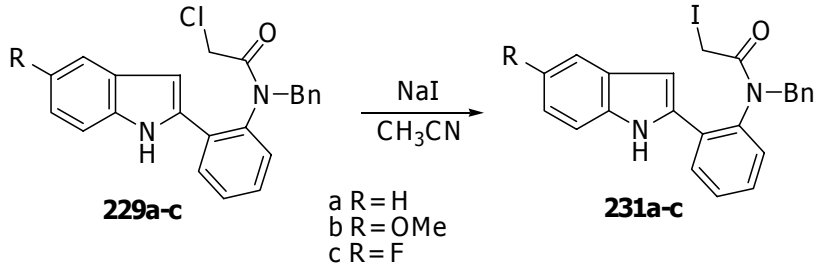
The HRCI-MS of **229a** gave a peak at *m/z* 375.1267 (MH^+) consistent with the molecular formula $C_{23}H_{20}N_2O^{35}Cl$ and corresponding to the addition of a chloroacetyl group to the starting material. The chloroacetyl methylene protons were obvious in the ^1H NMR spectrum of the product, by two doublet signals at 3.74 ppm and 3.87 ppm with a coupling constant of 13.2 Hz. In the ^{13}C NMR spectrum signals at 42.4 ppm and the carbonyl carbon at 166.8 ppm were ascribed to the methylene carbon and carbonyl group respectively of the chloroacetamide functionality.

Even though this reaction was a shorter route to the chloroacetamide, a large amount of 2-(2′-aminophenyl)-1*H*-indole **212a** remained in the initial reaction mixture due to the need to ensure monoalkylation predominated. Also it should be noted that only **212a** is commercially available, and a range of substituted 2-(2′-aminophenyl)-1*H*-indoles were required in this study.

3.4.3 Preparation of iodoacetamides

As discussed previously in Chapter 2, iodine is a better group than chlorine and a better group for the free radical cyclisation of haloacetamides. In this research, we were

interested in the construction of various *N*-substituted paullone derivatives, therefore, the *N*-benzylchloroacetamides **229a-c** were converted to the *N*-benzyliodoacetamides **231a-c**.



229a-c **231a-c**

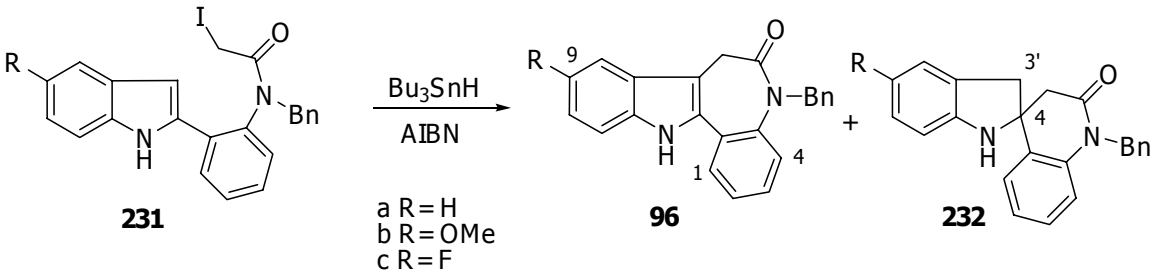
Scheme 3-19. General procedure for the preparation of iodoacetamides.

Synthesis of the *N*-benzyliodoacetamide **231a** by stirring with NaI in CH_3CN at room temperature[94] for 12 hours gave the desired product in 92% yield. The reaction was quite clean and the product was purified by passing through a short silica column. The HRCI-MS of **231a** gave a peak at *m/z* 467.0612 (MH^+) consistent with the molecular formula $C_{23}H_{20}N_2OI$. The ^1H NMR spectrum of **231a** showed the presence of two doublet signals at 3.49 ppm and 3.59 ppm ascribed to the methylene protons, which moved upfield relative to those in the starting material. In the DEPT spectrum, a new signal was observed at -1.9 ppm[87] which was assigned to the iodoacetyl methylene carbon. The signal ascribed to the methylene carbon moved dramatically upfield from those in the starting chloroacetamide (42.4 ppm) indicating that the iodide exchange was successful.

The reaction of both iodoacetamide **231b** and **231c** were conducted using the same methodology as that for **231a** and resulted in clean reactions with only the desried iodoacetamide products being obtained. The products were identified by their characteristic signals ascribed to the methylene group in both the ^1H NMR and ^{13}C NMR spectra.

3.5 Radical cyclisations

As part of our interest in the formation of indole fused seven membered ring systems, the iodocetamides **231a-c** were treated with Bu_3SnH and AIBN to undergo free radical cyclisation, leading to the paullone derivatives **96** (Scheme 3-20). The results are shown in Table 3-3.



Scheme 3-20. Radical cyclisation of iodoacetamides 231a-c.

Table 3-3. Radical cyclisation of 231a with Bu_3SnH, AIBN in boiling solvents.

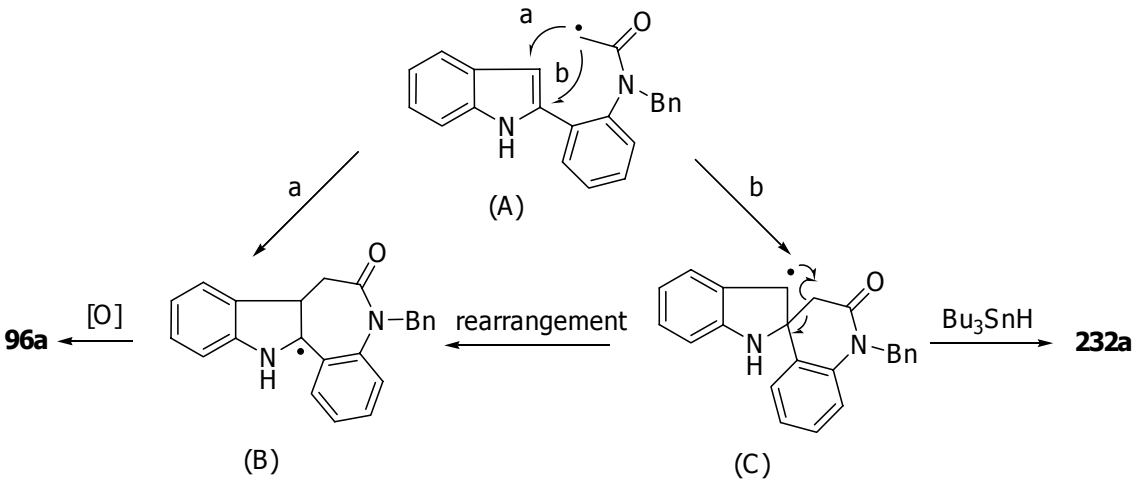
Entry	mmol	Solvent	Yield (%)	
			96a	**232a**
1	0.13	Toluene	25	-
2	0.15	Toluene	8	13
3	0.36	Toluene	-	10
4	0.13	Mesitylene	52	-

The initial reaction of **231a** with Bu_3SnH and AIBN in boiling toluene afforded the indole fused seven-membered ring compounds **96a** in 25% yield and some other unidentified compounds. The HRCI-MS of **96a** gave a peak at *m/z* 339.1498 (MH^+) consistent with the molecular formula $C_{23}H_{19}N_2O$ which indicated the loss of a hydrogen

and iodine atom from the starting material. The ^{1}H NMR spectrum of **96a** indicated the loss of the indolic H-3 proton and the presence of two doublet signals ascribed to the methylene protons (H-7) at 3.37 ppm and 3.73 ppm. The gHSQC spectrum confirmed the methylene signal for C-7 at 35.5 ppm. In the gHMBC spectrum, H-7 gave cross peaks with the indole carbons, which confirmed the cyclisation onto the indole ring.

In an attempt to optimise the yield of **96a**, the reaction was repeated using the same conditions, but using de-gassed toluene as a solvent. The yield of **96a** was reduced from 25% to 8%, however, and a new spiro compound **232a** was obtained in 13% yield. The structure of the spiro compound **232a** was comfirmed by NMR spectroscopy and mass spectroscopic analysis. In the ^{1}H NMR spectrum, two doublet signals were observed at 2.89 ppm and 3.09 ppm which were ascribed to the methylene protons (H-7). In addition, another group of signals, apart from those for the benzylic protons, were observed as two doublets at 3.03 ppm and 3.31 ppm and were ascribed to the methylene protons (H-13) on the indoline ring system. A broad singlet at 3.95 ppm, which was ascribed to the NH proton, indicated that the aromaticity of the pyrrole ring component in the indole had been destroyed. The DEPT, gHSQC and gHMBC experiments enabled the ^{13}C NMR spectrum assignment. The DEPT spectrum of **232a** indicated the presence of methylene carbons ascribed to C-3 and C-3´ at 42.4 ppm and 46.3 ppm, respectively. The position of H-3 was confirmed from the gHMBC spectrum. The methylene H-3 protons have a cross peak with the carbonyl carbon while the H-3´ protons did not have a cross peak with the carbonyl carbon.

Possible mechanisms for the formation of the spiro compound **232a** and the paullone **96a** are outlined in Scheme 3-21. The carbon-centred radical intermediate (A) from the iodoacetamide and $Bu_3Sn^{\cdot}$ could undergo cyclisation via two different pathways.



Scheme 3-21. Proposed mechanism for the formation of the paullone 96a and the spiro compound 232a

Addition of the carbon-centred radical at the indolic C-3 position via pathway a, a 7-*endo-trig* process, would give the seven membered ring fusion and a new carbon centred radical intermediate (B) at C-2. Alternatively, radical cyclisation at the indolic C-2 position (pathway b), a favoured 5-*exo-trig* process, would give the six membered ring spiro radical intermediate (C). Rearrangement of the radical could also afford the fused radical species (B); migration of the acyl alkyl group rather than the aryl group might be expected in this rearrangement process as a result of benzylic stabilisation of the incipient tertiary radical. It should be noted however that at ordinary temperatures alkyl groups do not normally undergo 1,2-free radical rearrangements. However, in this case a relatively higher temperature is involved (mesitylene; b.p. 163-165 °C), and the alkyl-acyl moiety may also tautomerise to an enol which then rearranges; 1,2-migration of vinylic groups is known to occur readily in acyclic systems.[155]

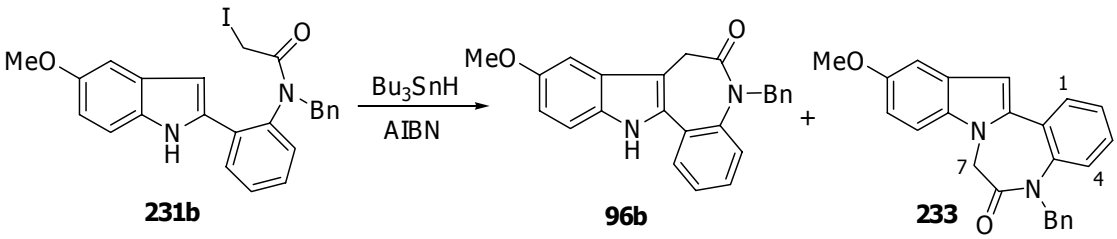
The fact that no **232a** was observed when the reaction was conducted at a higher temperature in boiling mesitylene is consistent with a significant activation energy barrier for this rearrangement. At lower temperatures (boiling toluene), hydrogen abstraction by

(C) from Bu_3SnH to afford the spiro compound **232a** could be competitive with the rearrangement. The lack of formation of any spiro compound **232a** from the first reaction attempted in toluene is difficult to explain. The possible reason for the observation of **232a** in de-gassed toluene (Table 3-3, entry 2) may be that the hydrogen abstraction step from (C) does not have to compete with the reaction of (C) with oxygen, and also more (C) would be produced as any reaction of (A) with oxygen would be minimised.

In an attempt to increase the yield of **96a** and **232a**, and in order to investigate the effect of temperature on the rearrangement of the spiro compound to the paullone derivative, a larger scale reaction of **231a** was attempted in boiling toluene. However, only a 10% yield of the spiro compound **232a** was obtained together with a number of unidentified products; the cyclised seven membered ring product **96a** was not observed in the ^1H NMR of the mixture. The decrease in yield of the cyclised product was probably due to a competing reaction with oxygen in this case.

The spiro compound **232a** is representative of a new heterocyclic ring system. A related 5-*exo*-*trig* spirocyclisation of a carbon centred radical onto the C-2 position of indole, resulting in dearomatization after hydrogen abstraction, has been reported recently.[156]

The cyclisation reactions of iodoacetamides **231b** and **231c** with Bu_3SnH and AIBN in boiling mesitylene were then investigated. Using the same conditions as for **231a**, the reaction of **231c** gave a fair yield of the paullone derivative **96c** (45%). The reaction of **231b** gave a low yield the paullone derivative **96b** (25%), but cyclisation onto the indole nitrogen was also observed in this case with the indolo[1,2-*d*][1,4]benzodiazepin-6-one, compound **233** being obtained in 30% yield (Scheme 3-22).



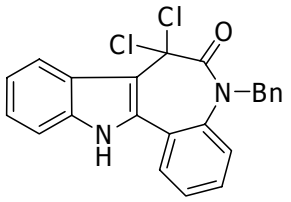
Scheme 3-22. Intramolecular cyclisation of iodoacetamide 231b

The structures of products **96b** and **96c** were elucidated on the basis of the signals characteristic of the two methylene groups in each case, and the absence of signals which could be ascribed to an indolic 3-CH group in both the ^{1}H NMR and ^{13}C NMR spectra. The HREI-MS of **233** gave a peak at *m/z* 368.1529 (M^{+}), consistent with the molecular formula of **96b**. In the ^{1}H NMR spectrum of **233**, two doublet signals ascribed to the methylene group in the 7-membered ring appeared at 5.01 ppm and 5.10 ppm, significantly downfield compared with the corresponding methylene group signals at about 3.30-3.90 ppm in **96b**. The absence of a broad signal which could be ascribed to the indole NH proton indicated that the downfield shift of the signals ascribed to the methylene protons was due to the formation of a new C-N bond to the indolic introgen.

The indolo-benzodiazepines of type **223** have been reported previously[157] via the reaction of the corresponding chloroacetamides and sodium hydride. However, in the work in this thesis, no base was necessary probably due to the electron donating properties of the methoxy substituent.

In an effort to access more highly functionalised paullone derivatives, cyclisation of the trichloroacetamide **230** was also investigated using the same conditions as for **231a** by treatment with Bu_3SnH and AIBN in mesitylene at reflux for 16 hours. However, EI-MS

analysis of the crude reaction product showed no trace of a signal at *m/z* 406 which would be expected for the cyclised product **234**.



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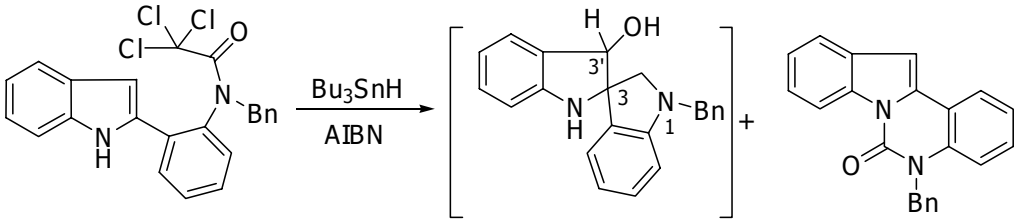


230 **235** **226a**

Scheme 3-23. Radical cyclisation of the trichloroacetamide 230.

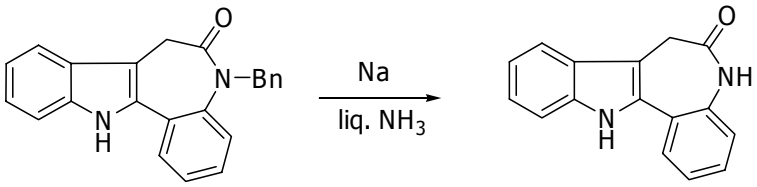
Purification of the reaction products by column chromatography gave two major fractions. The first fraction was obtained in 11% yield and the HRCI-MS spectrum gave a peak at *m/z* 329.1643 (MH^+). The second fraction was also obtained in 11% yield and the EI-MS spectrum gave a peak at *m/z* 324 (M^+), which was consistent with the loss of the CCl_3 group from the starting material. The ^1H NMR spectrum indicated this latter product was **226a**.

A tentative structure of **235** was assigned to the other product from the reaction as shown in Scheme 3-23. Since only a small amount of coumpound **235** was obtained, the tentative structure of **235** was assigned based on only HRCI-MS and nanoprobe NMR spectroscopy. The HRCI-MS indicated the formula $C_{22}H_{21}N_2O$ and the structure was determined by NMR spectroscopic experiments. In the ^1H NMR (CD_3CN) spectrum of **235**, two doublet signals, apart from those for the benzylic protons, were observed at 3.60 ppm

and 3.93 ppm and were ascribed to the methylene protons (H-2). Broad signals at 4.18 ppm and 5.01 ppm were ascribed to the OH and NH groups, respectively. The upfield shift of the NH proton indicated the loss of the aromaticity of the pyrrole ring component in the indole. A singlet signal ascribed to the methine proton in the 3´-position appeared at 6.48 ppm, significantly downfield from the corresponding indoline proton singals at about 3.0-4.0 ppm. The gCOSY, gHSQC, gHMBC experiments enabled the ^{13}C NMR spectrum assignments. There was no carbonyl signal observed in the ^{13}C NMR. The gHSQC spectrum of **235** indicated the presence of the methylene protons ascribed to C-2 at 33.0 ppm, while the methine proton was connected to a carbon signal at 71.6 ppm. A signal at 65.9 ppm, which had no cross peaks with any protons, was assigned as the quaternary carbon at C-2´ from the gHMBC long range carbon coupling experiment. Mechanistically it is not clear however how **235** may be formed and the structure remains a tentative one.

3.6 Debenzylation

In order to access the paullone system itself in which the lactam moiety is not *N*-substituted, the feasibility of chemoselective *N*-debenzylation with sodium in liquid ammonia was investigated. The debenzylation reaction was performed by the general method described in Lizos *et al*.[118] Paullone derivative **96a** was treated with metallic sodium in liquid ammonia for 10 minutes to afford the known[77] paullone **96** in 40% yield. There were no signals observed for the benzylic protons in the ^{1}H NMR spectrum of **96**, while the other signals observed were consistent with the debenzylated structure and were identical to those reported by Kunick.[77]



96a **96**

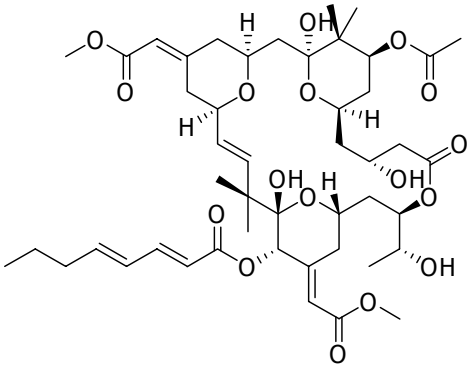
3.7 Summary and Conclusions

It has been shown that free radical cyclisation of indolyl iodoacetamide derivatives is a viable new approach to the pharmacologically significant paullone ring system. New palladium-mediated methodology for the construction of 2-(2′-aminoaryl)indoles has also been developed as part of this work. Both this methodology and free radical cyclisation have the potential for synthesis of a variety of new paullone analogues and derivatives.

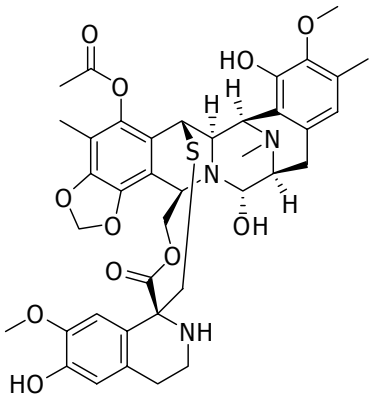
4 Synthetic approach to the marine natural product iheyamine A

4.1 Introduction

Marine natural products have emerged over the past 25 years as one of the richest sources of bioactive secondary metabolites.[4] In 2002, 677 new compounds were isolated and characterised from marine sources, together with their relevant bioactivities including indications of possible utility as anticancer, antibacterial, or cardio-vascular agents.[158] A significant number of marine natural products are currently in preclinical and clinical trials, and many of these are anti-cancer agents.[159] Such compounds that are in drug development programs included bryostatin 1 (**236**), a macrocyclic metabolite isolated from a Japanese bryozoan, *Bugula neritina*.[160] Bryostatin 1 inhibits protein kinase C and has been developed to treat melanoma, non-Hodgkins lymphoma, and renal cancer and is currently in phase 2 clinical trails.[159] Ecteinascidin 743 (**237**) is an isoquinoline derivative from the ascidian *Ecteinascidia turbinate*[161,162] and is undergoing human clinical trials as an antitumour agent; it is predicted to be approved as a novel drug soon.[163]



236 Bryostatin 1



237 Ecteinascidin 743

As many marine organisms are soft bodied, they have evolved the ability to synthesise toxic compounds in order to protect themselves from predators or to paralyse their prey. Such biologically active compounds might be useful for humans for the treatment of many human diseases, although, many marine organisms have so far only been explored to a very limited extent.[163,164] Therefore, a continued search of marine organisms for their biological diversity is expected to give rise to potential drugs with greater potency and efficiency.

Recently, the isolation of novel compounds from the ascidian, *Polycitorella* sp. (Figure 4-1), collected from the island of Iheya, Okinawa, Japan, has been reported.[20] These compounds were iheyamine A (**21**) and B (**22**), which have a new polycyclic heteroaromatic system containing a bis-indole fused azepine system. Both compounds exhibited moderate cytotoxic activity against P388, A549 and HT29 cell lines.[20]

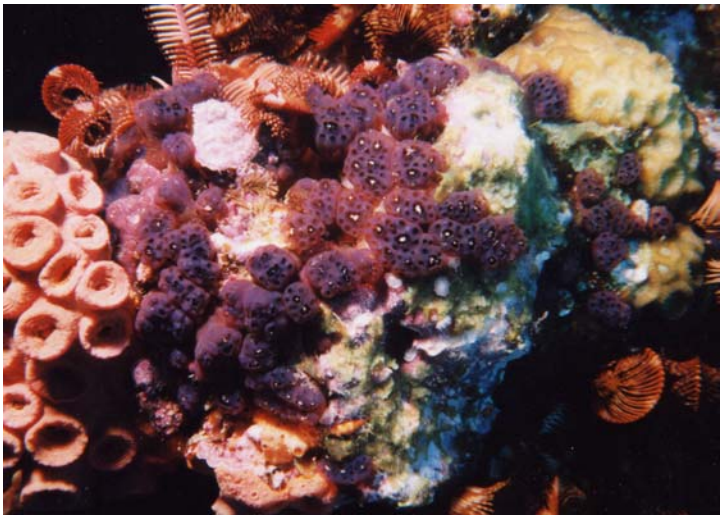
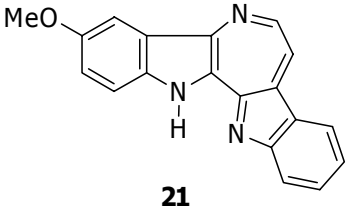


Figure 4-1. A colonial ascidian, *Polycitorella* sp. (purple)



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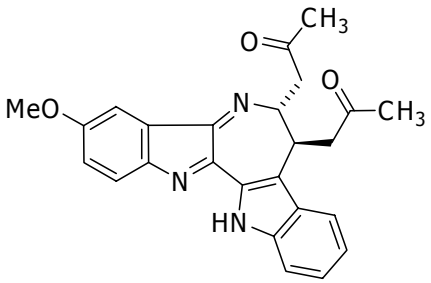

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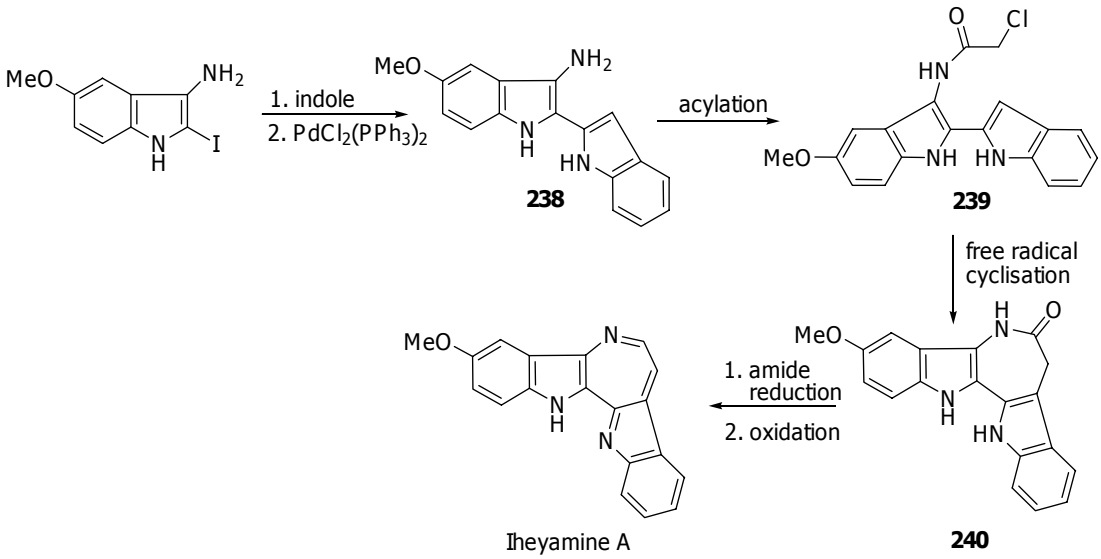
The yields of these iheyamines obtained from the ascidian were low, and in order to provide enough material to perform further biological studies, a synthetic route to the iheyamines was considered. In particular, this study focussed on approaches to iheyamine A and a demethoxylated analogue.

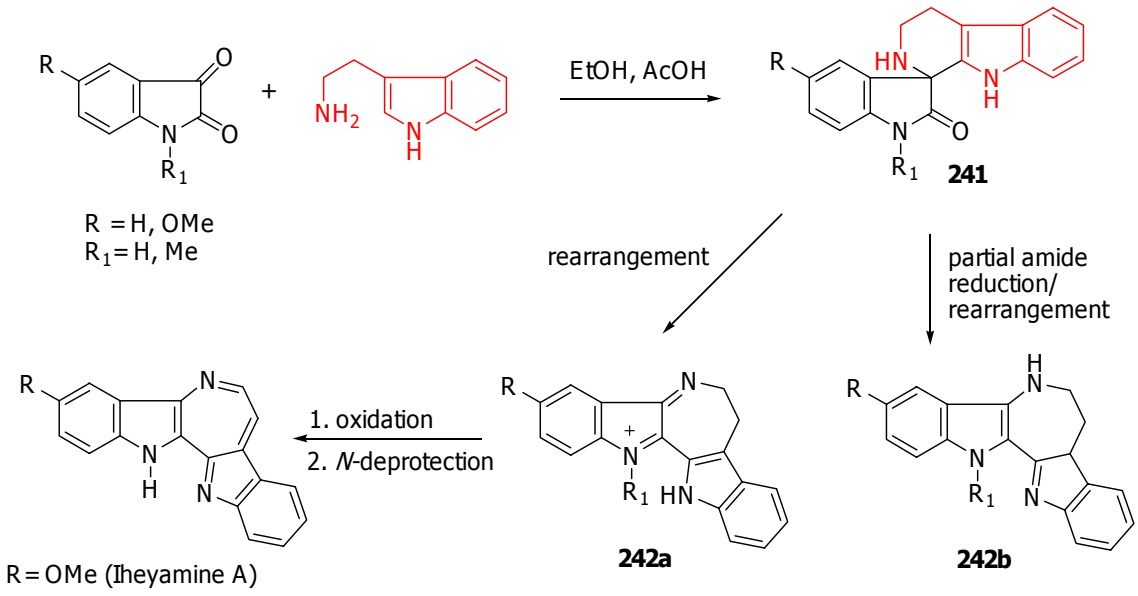
4.2 Proposed synthetic routes

Two methods for the synthesis of iheyamine A were proposed. The first approach involved an intramolecular free radical cyclisation of the key haloacetamide intermediate **239** to form the bis-indole fused seven-membered ring **240** (Scheme 4-1). The key intermediate **239** could be prepared by a palladium catalysed cross coupling reaction of a 2-iodoindole and indole. The resulting bis-indole **238** could then undergo chloroacetylation to give the haloacetamide **239**. Partial amide reduction followed by oxidation might then be expected to provide access to iheyamine A.



Scheme 4-1. Proposed synthetic route to iheyamine A via radical cyclisation.

The second approach proposed involved the acid-catalysed rearrangement (together with elimination) of the spiro intermediate **241** to afford the required fused seven-membered ring system **242a** or **242b** (Scheme 4-2). The spiro intermediate **241** could be prepared by the condensation of the appropiate isatin and tryptamine, possibly mimicking part of the iheyamine biosynthetic pathway. Rearrangement of **241** might be expected to give compound **242a**, which could then undergo oxidation and deprotection to give the desired iheyamine A or its demethoxylated analogue. Partial amide reduction of **241** followed by rearrangement might also be expected to provide iheyamine A or its demethoxylated derivative.



Scheme 4-2. Proposed synthetic route to iheyamine A via spiro rearrangement.

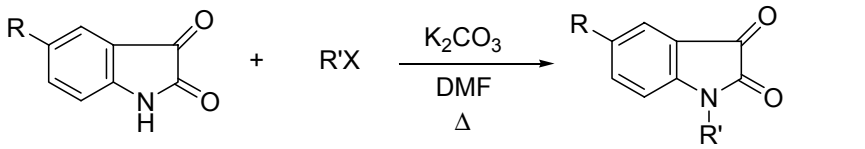
The second approach seemed to be the most feasible method in terms of the availability of starting materials and the direct and straightforward nature of the route. Therefore, the approach to the synthesis of iheyamine A concentrated on this second approach.

4.3 Synthesis of *N*-substituted isatins

Many methods have been devised for the *N*-alkylation of isatins. These derivatives are commonly synthesised from the reaction of the sodium or potassium salt of the isatin with alkyl halides or sulfates.[165] Various methods for the preparation of this salt have been reported, and these include the reaction of isatin with sodium hydride in DMF[166] or the use of potassium carbonate in either DMF (with microwave irradiation)[132] or in acetone.[167] In the latter case, an aldol reaction of the solvent also occurs with a carbonyl group of the isatin derivative.

In the preparation of 1-methylisatin, literature[167,168] reports suggested that only moderate yields were obtained. However, 1-methylisatin can be obtained commercially from Sigma-Aldrich Ltd. at a reasonable price.

In the research described in this thesis, the 5-methoxyisatins were reacted with alkyl halides in the presence of anhydrous K_2CO_3 in DMF at reflux for 10 hours and the *N*-alkylated products were obtained in moderate to high yields (Scheme 4-3).



243a R= OMe, R'= Me
243b R= OMe, R'= allyl

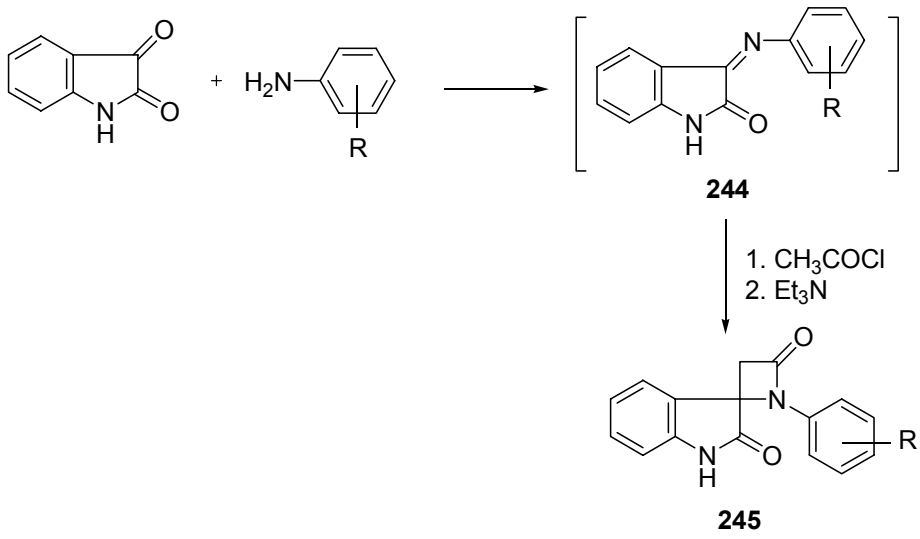
Scheme 4-3. Reaction of isatins with alkyl halides.

The reaction of 5-methoxyisatin and methyl iodide in the presence of anhydrous K_2CO_3 afforded the desired *N*-methylated product **243a** in 67% yield. In a similar manner, the alkyaltion of 5-methoxyisatin with allyl bromide afforded 1-allyl-5-methoxyisatin **243b** in high yield (99%). The *N*-allyl group was introduced as a potential alternative nitrogen protecting group in the synthesis. Evidence for the successful *N*-alkylation in each case was obtained from NMR spectroscopy and mass spectrometric analysis of the products. The ^{1}H NMR spectrum of **243a** revealed the absence of a broad signal expected for the isatin NH and the presence of a signal resonating at 3.21 ppm ascribed to the *N*-methyl protons. The corresponding methyl carbon signal was also observed in the ^{13}C NMR spectrum at 26.5 ppm. This data suggested that successful methylation of the isatin NH had occurred and there was further confirmation from HREI-MS, which showed a molecular ion at *m/z* 191.0583, consistent with the formula $C_{10}H_9NO_3$ which correlated with the desired product.

Similarly in the ^{1}H NMR spectrum of **243b** no signal for the indolic NH proton was present, but a doublet signal at 4.34 ppm, two doublet signals at 5.29 (*J*= 11.5 Hz) and 5.32 (*J*= 11.0 Hz) ppm and a multiplet at 5.84 ppm were indicative of the presence of the allylic group. The ^{13}C NMR spectrum also showed resonances at 42.7 and 112.2 ppm ascribed to the methylene carbons and a resonance at 130.8 ppm ascribed to a methine carbon consistent with this group. The structure of **243b** was also confirmed by the HREI-MS. The mass spectrum gave a molecular ion at *m/z* 217.0739, which was consistent with the molecular formula $C_{12}H_{11}NO_3$ of the *N*-allylated product.

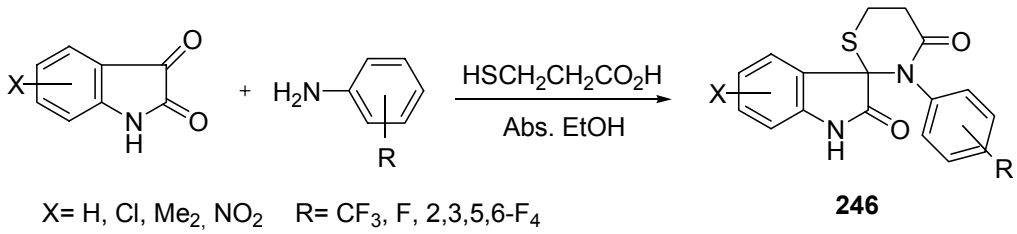
4.4 Synthesis of spiro compounds

Isatin and its derivatives can undergo nucleophilic attack at the C-2 and/or C-3 position. The chemoselectivity of these reactions depends on the nature of the nucleophiles, on the nature of the substituents attached to the isatin nucleus and especially on those bonded to the nitrogen atom, as well the solvent and temperature employed.[169] Nucleophilic substitution at the C-3 position may be followed by a spiro-annelation process at position C-3 if a second nucleophilic group is present to give a spiro compound.[170,171] This process may also involve the addition of a separate nucleophile followed by cyclisation with elimination. As an illustration of this spiro ring approach, condensation of isatin with aromatic amines in toluene afforded the intermediate isatin-3-anils **244**, which cyclised *in situ* with acetyl chloride in the presence of base to give (Scheme 4-4) the fungicidal 1′-phenylspiro[indole-3,4′-azetidine]-2-(3*H*),2′-diones **245**.[172]



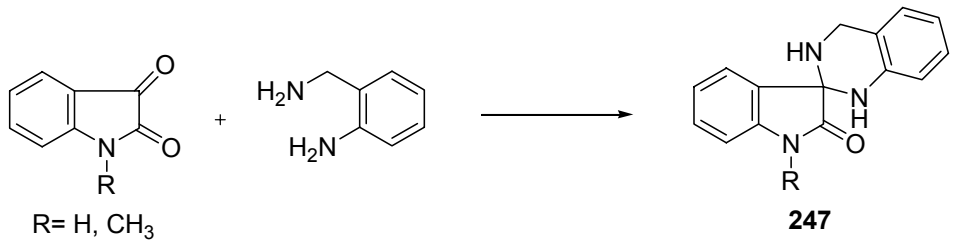
Scheme 4-4. Formation of the 1′-phenylspiro[indole-3,4′-azetidine]-2-(3*H*),2′-diones 245.

A similar approach (Scheme 4-5) was also used to synthesise the spiro[indoline-3,2′-[1,3]thiazinane]-2,4′-diones **246**.[173]

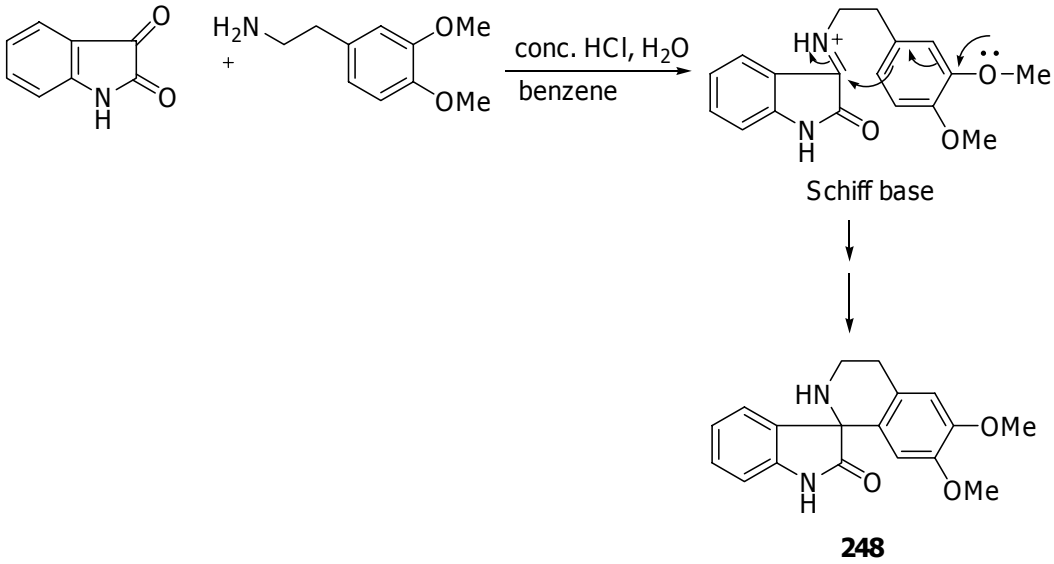


Scheme 4-5. Synthesis of the spiro[indoline-3,2′-[1,3]thiazinane]-2,4′-diones 246.

The construction of the spiro ring system may also involve the second nucleophilic group from the same molecule. Examples of this approach include the formation of the spiro compounds **247**,[174] which were obtained as the sole products and none of the 2,3-condensation products or ring opening products were observed (Scheme 4-6), as well as the cyclisation of the Schiff base from 2-(3,4-dimethoxyphenyl)-ethylamine to afford the spiro compound **248**[175] (Scheme 4-7).

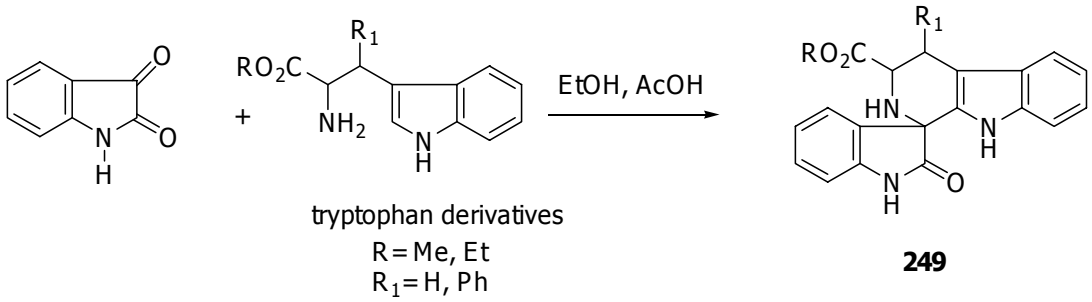


Scheme 4-6. A spiro-annelation formation.



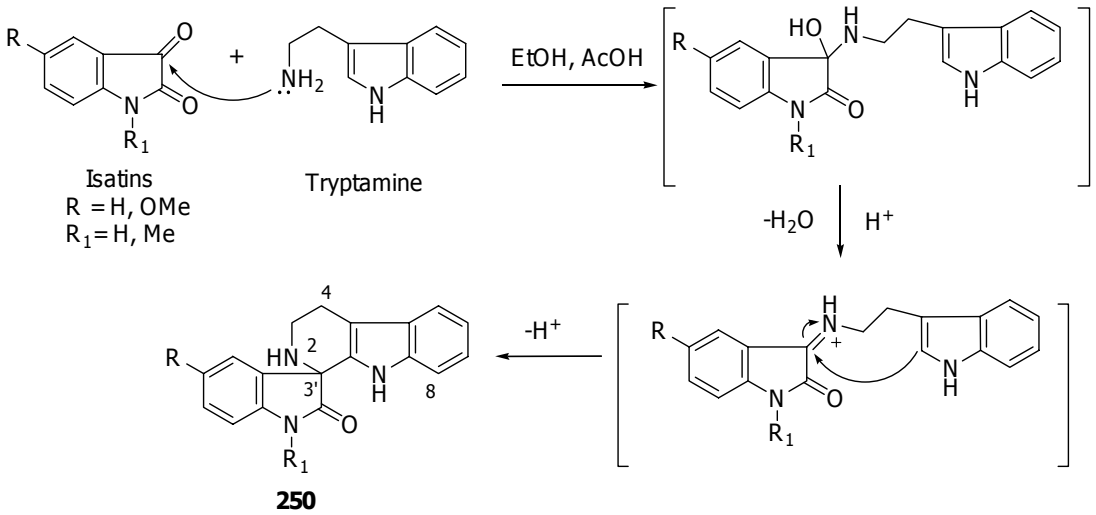
Scheme 4-7. Reaction between isatin and 2-(3,4-dimethoxyphenyl)-ethylamine.

The condensation of tryptophan derivatives with isatin has also been reported to form the spiro compounds **249** (Scheme 4-18).[176,177] Spiro compounds of type **249** are similar to the ones required for the proposed rearrangement reaction in the current study.



Scheme 4-8. Condensation of isatin with functionalised tryptophan derivatives.

Thus, the condensation of isatins and 1-alkylisatins with tryptamine in ethanol with glacial acetic acid as catalyst gave the corresponding imine derivatives which underwent further internal nucleophilic attack at C-3 to afford the spiro derivatives **250** (Scheme 4-9). A high yield (89%) was obtained when using *N*-unsubstituted isatin but when using *N*-methylisatins, the yields were reduced to around 55% (Table 4-1). The electron releasing methyl group may possibly help to stabilise the vinylogous amide-type resonance contributing structure involving the C-3 carbonyl group, thus making it less susceptible to nucleophilic attack.



Scheme 4-9. Mechanism for the syntheses of spiro derivatives.

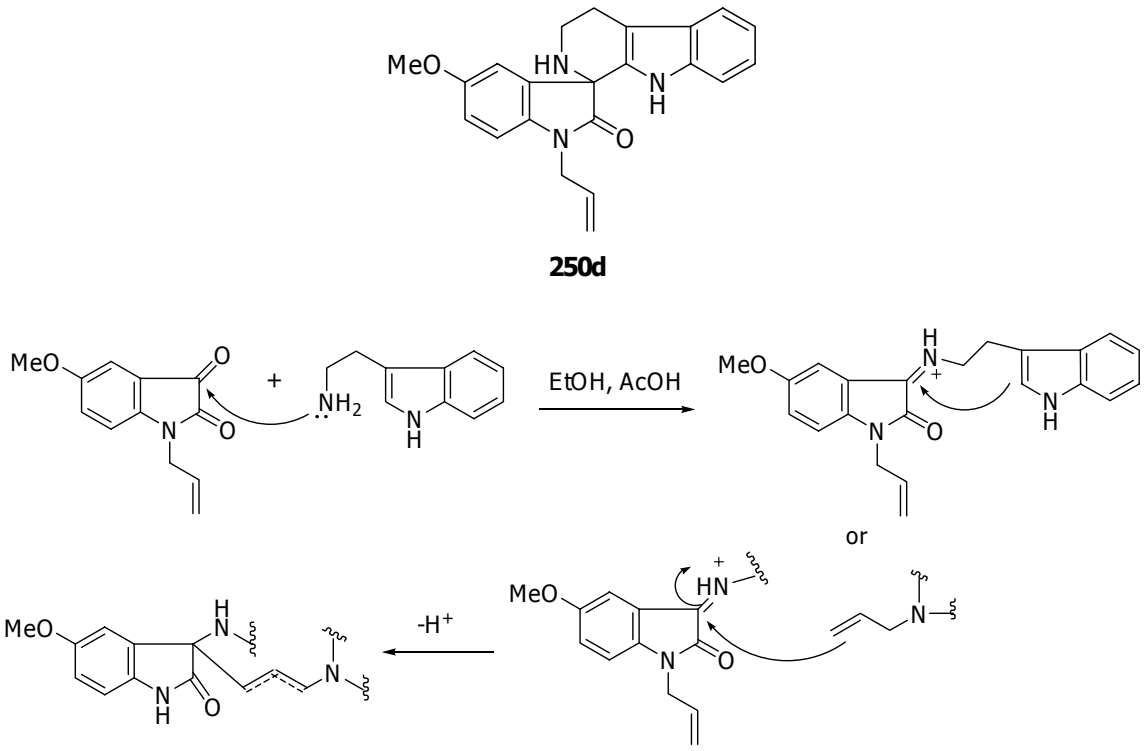
Table 4-1. Spiro product yields from reactions of various isatins with tryptamine.

Compound number	R	R´	Yield (%)
250a	H	H	89
250b	H	CH_3	54
250c	OMe	CH_3	56

The spiro products **250** were identified by their characteristic NMR signals and mass spectra, and by comparison of their spectra with those of the 3´-methoxycarbonyl analogue (compound **249**, R= Me, R´= H) which was described by Levy *et al*.[176] and Bizot-Espiard *et al*.[177]

In the ^{1}H NMR spectra of **250a-c**, the absence of any signal which could be attributed to an indolic H-2 proton was confirmatory evidence for spiro cyclisation involving this position. The ^{13}C NMR spectra of **250a-c** exhibited quaternary signals at 61.7-62.3 ppm which were ascribed to the carbon atom in the spiro centre in each case, as well as signals characteristic of those expected for the carbonyl carbons at 176.8-179.6 ppm. The HRMS of each product also supported the formation of the spiro moieties and gave a molecular formula consistent with the corresponding product in each case.

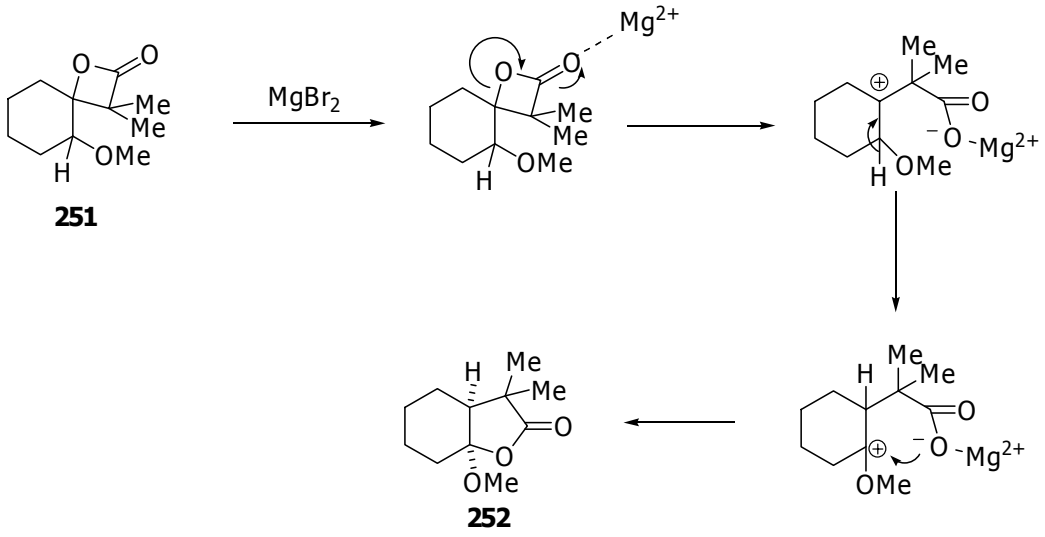
The attempted synthesis of the *N*-allyl spiro derivative **250d** was unsuccessful. Analytical TLC of the crude reaction mixture, unlike that from the reaction of the *N*-methylisatin, showed the presence of several products. This might due to competing reactions involving attack by the intermediate iminium ion on both the indole (intramolecularly) and the allyl group (intermolecularly) (Scheme 4-10). Purification by column chromatography was difficult and the mixture could not be successfully separated.



Scheme 4-10. Possible reactions in the synthesis of N-allyl spiro compound 250d.

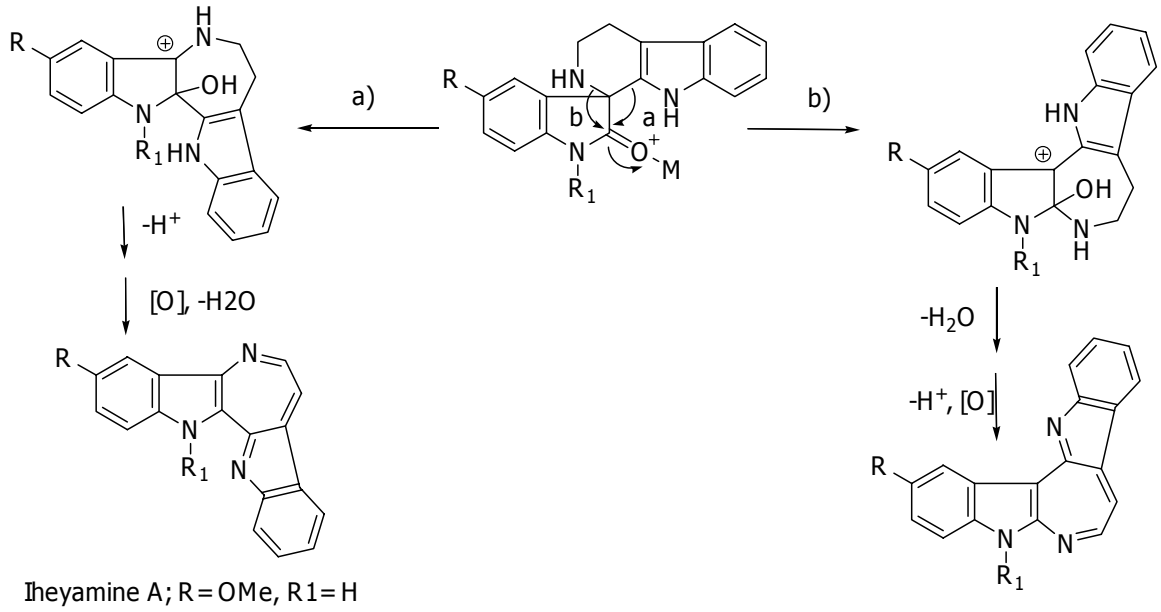
4.5 Attempted acid mediated rearrangement

Rearrangement of a spiro bicyclic molecule via migrating a bond from one atom to the adjacent atom can lead to a ring enlargement. Activation is required for this process to occur. For example, the rearrangement of the β-lactone **251** to the lactone **252** was achieved via the treatment of **251** with freshly prepared $MgBr_2$.[178] The ring transformation depends on both the relative stability of the two intermediate carbocations involved and the ability of the migrating bonds to achieve an antiperiplanar relationship with respect to one another to effect γ-lactone formation.



Scheme 4-11. The rearrangement of the β-lactone 251.

While rearrangement with ring enlargement of spiro compounds of type **250** has not been described previously, it was reasoned that a Lewis acid mediated process may be possible. Complexation of a Lewis acid to the lactam carbonyl group could provide the initial stimulus for such a rearrangement. However, there are two possibilities for this ring transformation depending on which bond adjacent to the spiro centre undergoes rearrangement to give the intermediate **253** (via pathway **a**) or **254** (via pathway **b**) (Scheme 4-12). Transformation via pathway **a** would ultimately give the required iheyamine A core nucleus, while migration of bond **b** would give an isomeric bis-indole fused azepine system. A preference for migration of bond **a** might be expected on the basis of extra charge stabilisation by the adjacent nitrogen (in **253**).



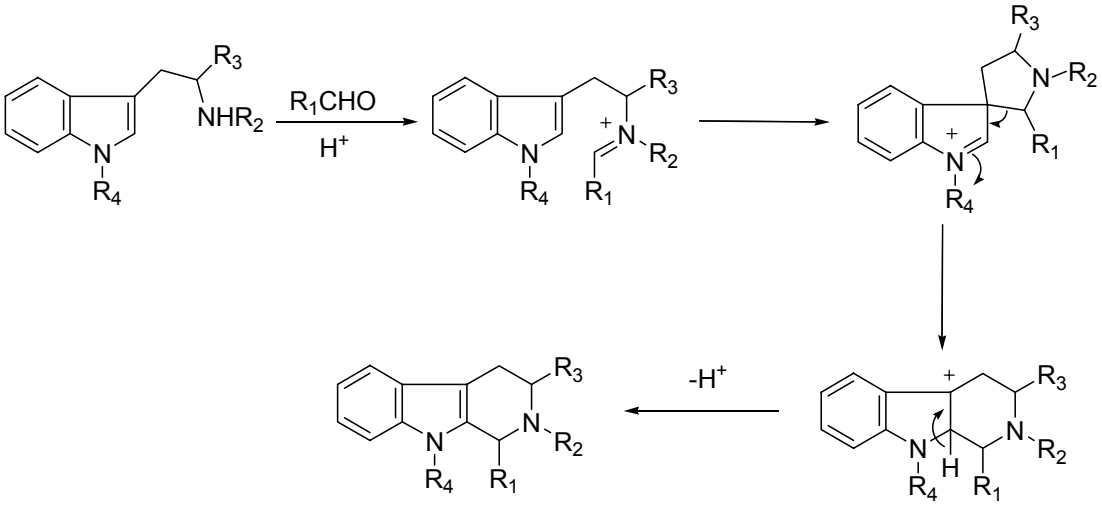
Scheme 4-12. Two possible pathways of the spirooxindole rearrangement.

In an attempt to give effect to the proposed transformation, reaction of the spirooxindoles **250b-c** with various Lewis acids including $MgBr_2$, $BF_3.Et_2O$, $In(OTf)_3$, and $Ti(OiPr)_4$ were investigated, as well as a reaction with the Brönsted acid, trifluoroacetic acid (TFA). Unfortunately, in all cases no rearrangement products were obtained and mainly unreacted starting material was recovered. Clearly complexing to the carbonyl oxygen of the spirooxindoles **250b-c** was insufficient to induce the spiro-rearrangement. In view of this, indoline intermediates were investigated.

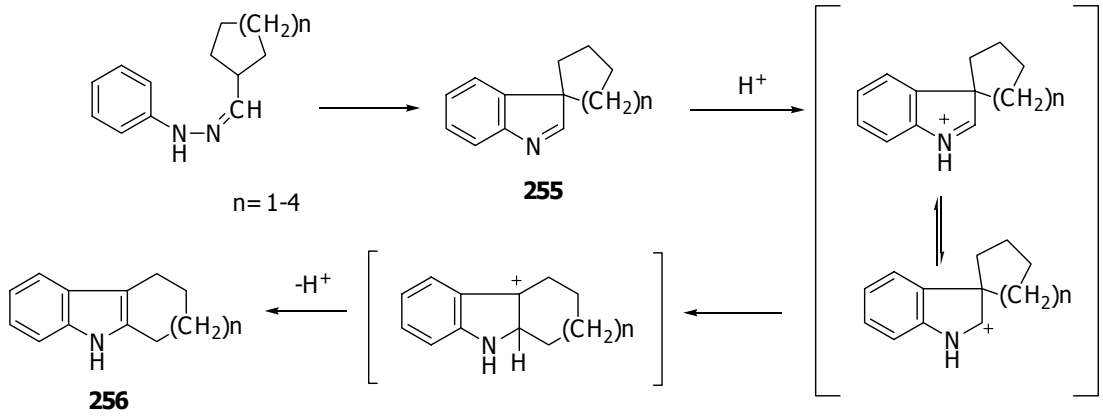
4.6 Rearrangement of spirocyclic oxindoles

The literature on the migration of 3,3-disubstituted indolenines to 2,3-disubstituted indoles indicated they are readily rearranged under acidic conditions and the substituent migration depended on relative migratory aptitudes.[179,180] Such a rearrangement of a

spiroindolenine is a central step in the formation of 1,2,3,4-tetrahydro-β-carbolines in the Pictet-Spengler reaction. Although a direct pathway involving electrophilic attack at position 2 of the indole ring system has been postulated, in general, the spiroindolenine intermediate was rearranged to the β-carbolines under mildly acidic conditions (Scheme 4-13).[181] A separate reaction using acid-catalysed rearrangement of the spiro[3*H*]indole was also investigated.[182] The spiro[3*H*]indoles **255**, obtained from the phenylhydrazones of the aldehydes by the Fischer method, were carefully treated with a sulfuric acid catalyst to obtain the cycloalkano[b]indoles **256** (Scheme 4-14). Thermal rearrangement of the spiro[3*H*]indole **255** (n= 2) in ethylene glycol to the cycloalkano[b]indole **256** (n= 2) in good yield (73%) was also observed. Ethylene glycol seems to behave as a mild protic acid catalyst in the reaction and the rearrangement can be rationalised by a similar mechanism to that shown in Scheme 4-14.

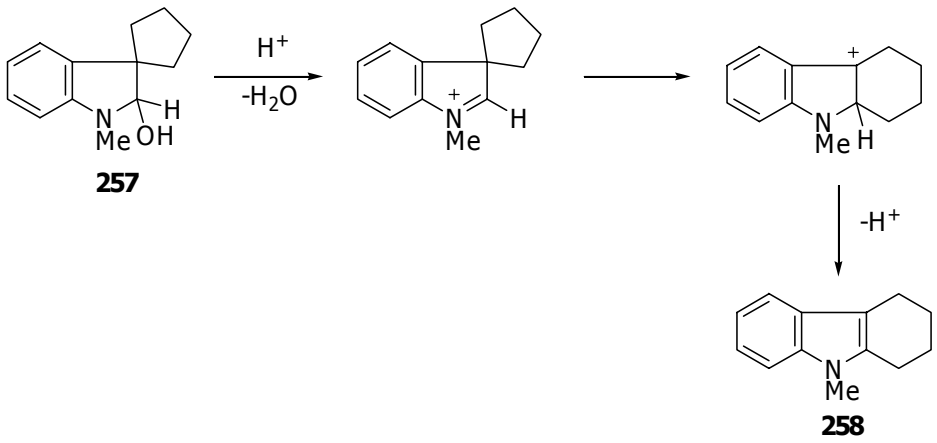


Scheme 4-13. The formation of β-carbolines via spiroindolenine intermediates.



Scheme 4-14. The rearrangement mechanism of the spiro[3*H*]indoles 255.[182]

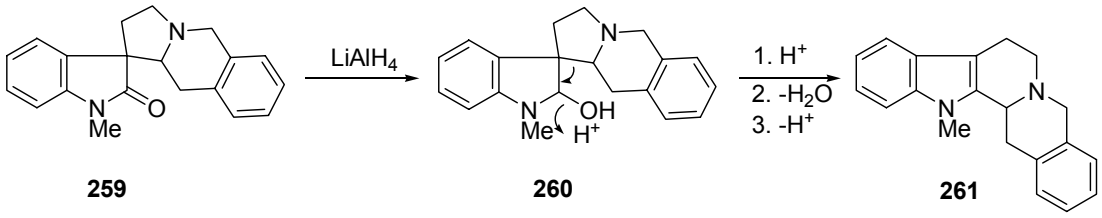
The presence of an aminal such as **257** (ie. –OH at C_2 of a dihydroindole) was found to have a profound effect on the ease of migration of substituent groups on the indole ring.[180] The rearrangement of indolinol **257** was initiated by the departure of a leaving group at C-2 by heating with concentrated hydrochloric acid or polyphosphoric acid to give the tetrahydrocarbazole **258** via the iminium ion intermediate.[183]



Scheme 4-15. Rearrangement of indolinol 257.

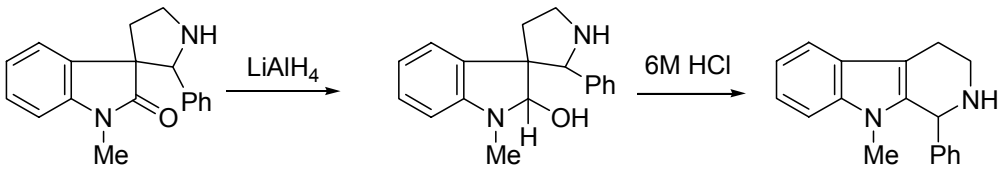
4.6.1 Preparation and rearrangement of carbinolamines

The conversion of oxindoles to indolinols (carbinolamines) can be achieved by partial reduction of tertiary amides. Lithium aluminum hydride (LAH) has proved to be very sensitive to amide groups; the use of excess of LAH generally yields the corresponding tertiary amine.[184] The partial reduction of the spirooxindole **259** with the calculated quantity of LAH gave indolinol **260** which, when treated with hydrochloric acid, afforded the β-carboline **261**.[185]



259 **260** **261**

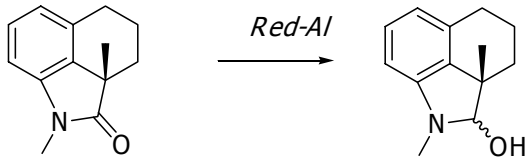
The conversion of the spirooxindole **262** to the β-carboline **264** fits into the same pattern of reactivity of rearrangement. Treatment of spirooxindole **262** with 0.5 equiv. LAH in ether gave the carbinolamine **263** in 51% yield.[179] The formation of the rearranged product **264** was achieved in cold 6 M HCl.



262 **263** **264**

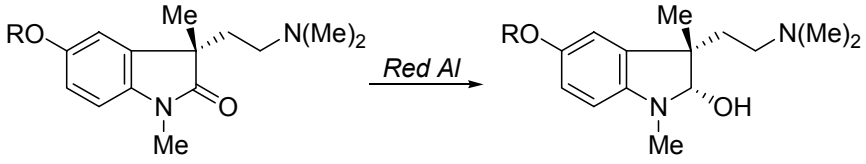
Although LAH has proved to be useful for the partial reduction of tertiary amides, it is sensitive toward air and is hazardous in large scale preparations because of its high flammablility and strong reducing properties.[186] The introduction of alkoxy substituents into the aluminium hydride moiety provides more selective reagents than LAH. For example, sodium bis(2-methoxyethoxy)aluminum hydride in toluene, known commercially

as *Red-Al*®, is stable to oxygen and is highly soluble in a variety of solvents; reactions are also easy to work up. It is a mild and safe reducing agent, especially for large scale reductions.[187] Recently, *Red-Al*® has been widely used, especially for the selective reduction of a number of tertiary amides.[188,189] Thus, Waldvogel *et al*.[188] reduced amide **265** with 1.2 equiv. of *Red-Al*® to obtain a mixture of two aminal (carbinolamine) diastereoisomers **266** in a ratio of 2:1.



265 **266**

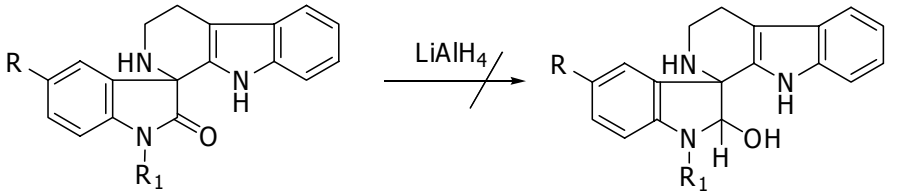
The reaction of *Red-Al*® with oxindole **267** reduced it stereoselectively to give the carbinolamine **268** in good yield.[189]



267 **268**

In view of these literature precedents, it was decided to investigate the reduction of the oxindoles **250a-c** to the carbinolamines **269a-b** and then assess their rearrangement under acidic conditions. Initially, reduction of oxindole **250a** with 0.5 equiv. of LAH in refluxing diethyl ether for 1 hour was attempted but this was unsuccessful (Scheme 4-16). Refluxing for 2-4 hours in this solvent was also unsuccessful. After work up of the reactions, only starting materials were recovered. The insolubility of oxindole **250a** in diethyl ether might be partly responsible for the lack of success. The addition of a small amount of THF to the reaction mixture in order to help solubility did not make any difference in the overall result. In addition, increasing the molar equivalence of LAH to 1.0 equiv. was also ineffective in

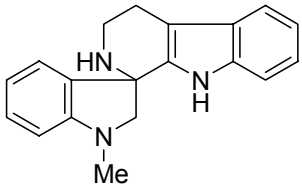
reducing the amides. An excess of LAH would be expected to fully reduce the oxindole **250a** to the indoline **270**.



250a R = H, R_1 = H
250b R = H, R_1 = Me

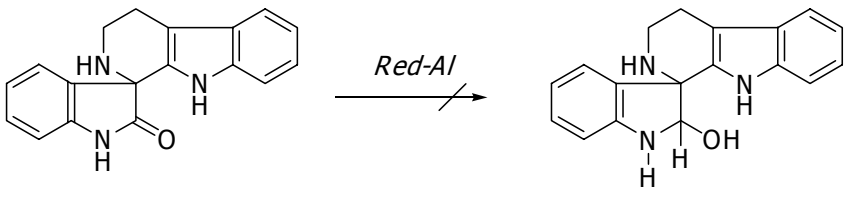
269a R = H, R_1 = H
269b R = H, R_1 = Me

Scheme 4-16. Attempted partial reduction of oxindoles 250a-b using $LiAlH_4$.



270

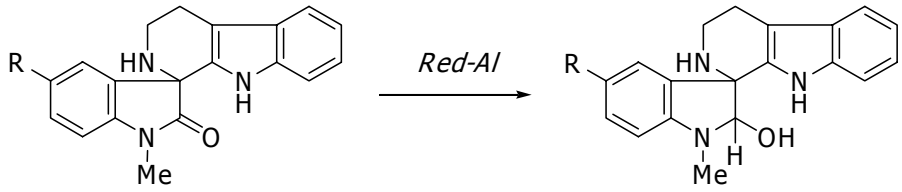
Reduction of oxindole **250a** with *Red-Al*® was then attempted (Scheme 4-17), based on a similar reaction described in the literature.[189] Analytical TLC monitoring of the reaction mixture over time showed only starting material present at each sampling point. No evidence for the desired product **269a** was detected in the LRMS of the reaction mixture, which would be expected to show a molecular ion signal at *m/z* 291 if successful partial reduction had occurred.



250a **269a**

Scheme 4-17. Attemped partial reduction of *N*-unsubstituted spirooxindole 250a

The partial reduction was reattempted using the *N*-methyl substituted oxindoles **250b-c** as starting materials. TLC analysis of each reaction indicated a new compound had formed which had a higher R_f than the respective starting material. Significant difficulty was experienced in purification of the reaction mixtures due to the instability of the products. However, relatively clean products were obtained eventually and they were analysed by ^{1}H NMR spectroscopy.



250b R = H
250c R = OMe

269b R = H
269c R = OMe

Scheme 4-18. Partial reduction of spirooxindoles 250b-c.

The ^{1}H-NMR spectra of these products showed singlet signals ascribed to the indolic H-2 protons at 4.88-4.96 ppm. The singlet signals ascribed to the methyl group resonated at 2.89-2.92 ppm, upfield of the corresponding signals in the starting materials. Such an upfield shift is consistent with reduction of the carbonyl group. For example, as shown in Figure 4-2, the ^{1}H NMR spectrum of **269b** revealed a singlet signal ascribed to the methyl group at 2.92 ppm, which had shifted upfield from 3.20 ppm in the starting material. The presence of a singlet signal ascribed to the indolic H-2 at 4.96 ppm was further confirmatory evidence for the partial reduction of the carbonyl group. The EI-MS spectra gave peaks at *m/z* 305 and 355 (M^+) for **269b** and **269c**, respectively, which indicated the reduction with *Red-Al*® had given the desired carbinolamine products.

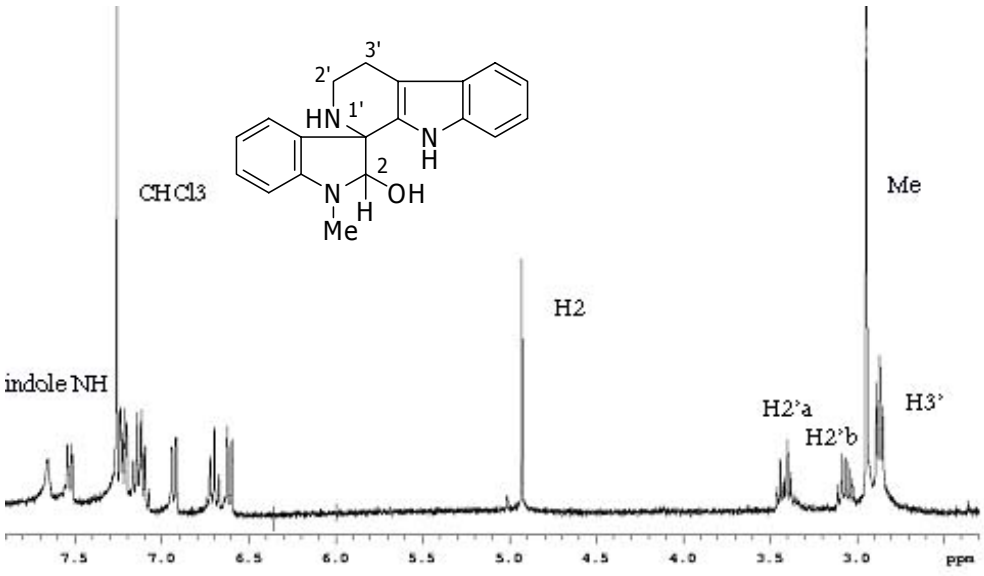
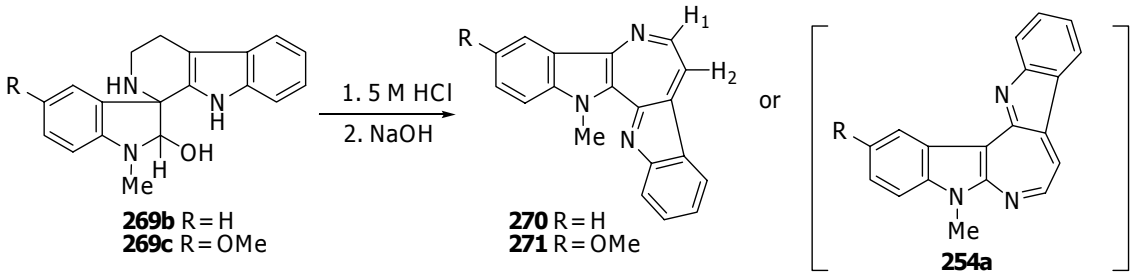


Figure 4-2. ^{1}H NMR spectrum of the carbinolamine 269b.

4.6.2 Rearrangement

The initial rearrangement involved the treatment of the carbinolamine **269b** with warm 5M HCl (Scheme 4-19). A precipitate was formed after basification with 25% KOH. Purification by column chromatography gave the rearrangement product **270** (17% yield over 2 steps from **250b**) along with unidentified baseline materials. An interesting feature of this product in the ^{1}H NMR spectrum was that all proton signals appeared in the aromatic region with the exception of the methyl group. This indicated that full aromatisation had also occurred while warming in hydrochloric acid (or on basification) since the reaction mixture was exposed to air.



269b R = H
269c R = OMe

270 R = H
271 R = OMe

254a

Scheme 4-19. Rearrangement of carbinolamines to fused indole seven membered rings.

The ^{1}H NMR spectrum of **270** as shown in Figure 4-3 revealed the absence of a singlet signal which could be ascribed to the indolic H-2 proton and the absence of a broad signal normally seen for the indolic NH; in the starting material **269b**, this signal appears at 7.72 ppm. The gHSQC spectrum confirmed the correlation of H-1 (doublet at 8.97 ppm, *J*= 6.3 Hz), with C-1 at 132.2 ppm, and also the correlation of H-2 (doublet at 8.39 ppm, *J*= 5.7 Hz) with C-2 at 120.1 ppm. The gCOSY spectrum confirmed that H-1 gave a cross peak only with H-2. The DEPT spectrum indicated no signals for methylene carbons in this molecule. In the gHMBC spectrum, a quaternary carbon resonating at 139.8 ppm showed cross peaks at δ 128.7 (C-13), δ 127.2 (C-16) and δ 28.7 (CH_3), consistent with the quaternary carbon being C-11. This data suggested that the rearrangement and aromatisation of the carbinolamine had occurred and there was further confirmation from the HRCI-MS data, which showed a molecular ion at *m/z* 284.1178, consistent with the formula $C_{19}H_{14}N_3$. It should be noted however that the isomeric structure **254a** (R= H) cannot be excluded on the basis of the spectroscopic evidence, although on mechanistic grounds (Scheme 4-12), structure **270** is predicted to be favoured.

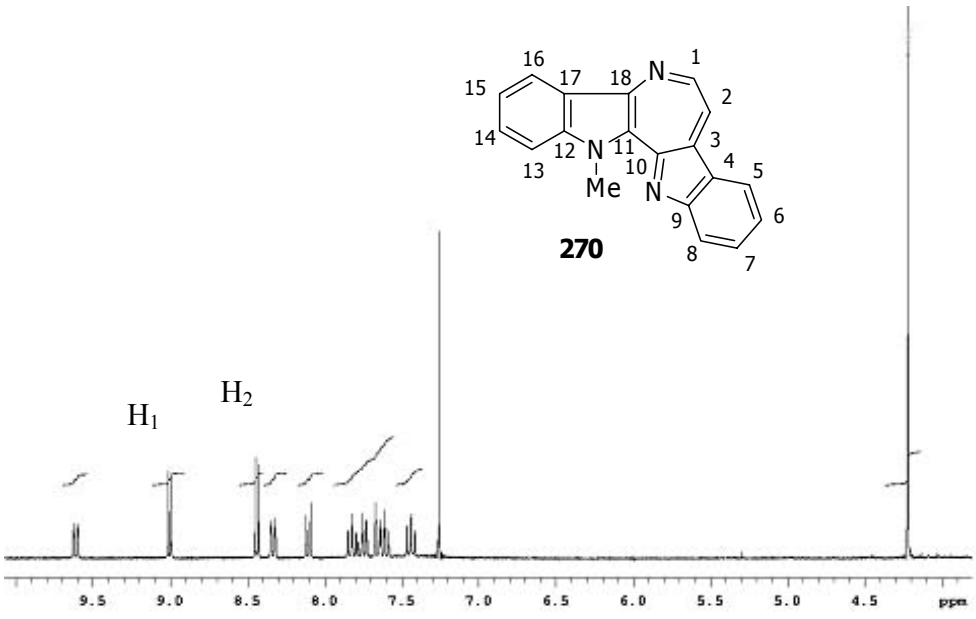
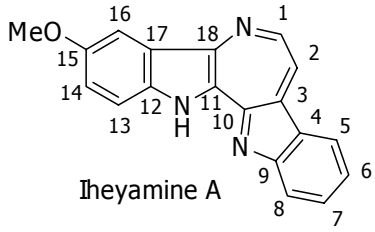
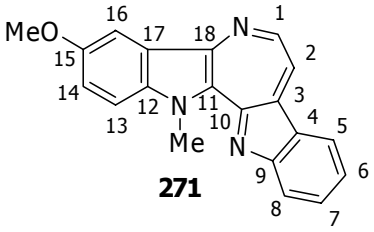


Figure 4-3. ^{1}H NMR spectrum of bis-indole fused seven membered rings 270.

The rearrangement was also attempted using the 5-methoxy carbinolamine derivative **269c** and the result indicated that the rearrangement product was obtained in 10% yield (over 2 steps). The structure was identified by the characteristic signals in the NMR spectrum and by comparison (Table 4-2) of the spectroscopic data (in $CDCl_3$) with those of iheyamine A as described by Higa *et al*.[20] The HREI-MS of this product also supported the formation of **271** and gave a molecular ion peak at *m/z* 313.1210, consistent with the formula $C_{20}H_{15}N_3O$ which correlated with the desired product.



Iheyamine A



271

Table 4-2. Comparison of ^{1}H NMR spectra of iheyamine A and 271

No.	^{1}H NMR [mult. *J* (Hz)] δ	
	Iheyamine A[20]	**271**
1	9.04 (d, 6.4)	8.96 (d, 5.4)
2	8.55 (d, 6.4)	8.50 (d, 6.0)
5	8.37 (brd, 7.9)	8.35 (d, 7.5)
6	7.52 (brdd, 7.9, 7.0)	7.52 (brdd, 7.5, 6.6)
7	7.74 (brdd, 7.9, 7.0)	7.80 (brdd, 8.1, 7.5)
8	7.86 (brd, 7.9)	8.14 (d, 8.4)
13	7.70 (d, 8.9)	7.58 (d, 8.7)
14	7.37 (dd, 8.9, 2.4)	7.37 (dd, 8.7, 2.4)
16	8.01 (d, 2.4)	7.98 (d, 2.4)
NMe	-	5.00 (s)
OMe	4.02 (s)	4.04 (s)

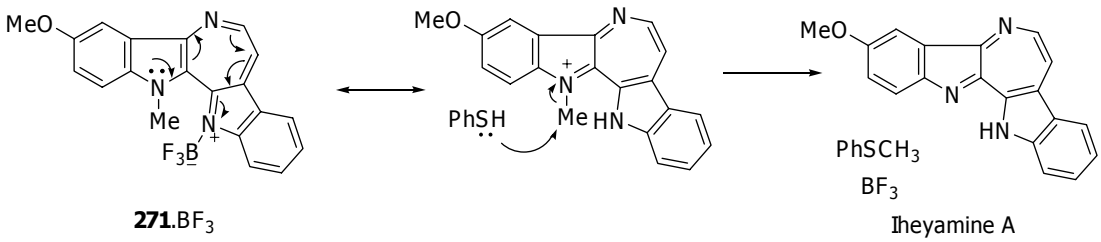
Compound **270** was also converted into its trifluoroacetate salt by treatment with trifluoroacetic acid. The ^{1}H NMR spectrum of the salt form of **270** showed two isomers were formed in a ratio of 2:1, on the basis of two singlet signals observed at 3.93 ppm and

4.01 ppm for the *N*-methyl groups. This suggested that protonation had occurred at one or both imine nitrogens. Recrystallisation of the mixture from ethanol gave no suitable trifluoroacetate salt crystals for X-ray crystallography.

4.7 Attempted *N*-demethylation

In order to complete the synthesis of iheyamine A, it was necessary to remove the *N*-methyl group from **271**. *N*-methyl groups exhibit good stability toward many kinds of reaction conditions, and the removal of the *N*-methyl protecting group often requires harsh reaction conditions resulting in less chemoselectivity.[190] The standard method employs chloroformates which is successful in the *N*-demethylation of aliphatic amines such as the demethylation of morphine.[191,192] Not unexpectedly perhaps, an initial attempt at demethylation of **270** using 2,2,2´-trichloroethylchloroformate was unsuccessful, due to the low nucleophilicity of the indolic nitrogen. TLC analysis of the reaction mixture over time showed only starting material present at each sampling point. No evidence for the demethylated product was detected by LR-MS analysis.

The demethylation was then attempted on **271** using thiophenol in the presence of boron trifluoride diethyl etherate ($BF_3.Et_2O$). The $BF_3.Et_2O$ was expected to complex with an imine nitrogen and thus assist demethylation by the thiophenol to give ultimately iheyamine A (Scheme 4-20).



Scheme 4-20. Attempted *N*-demethylation 271 using BF_3/thiophenol.

Exposure of **271** to $BF_3.Et_2O$ (1.5 eg) followed by PhSH (excess) in dry THF and heating at reflux for 3 days then resulted in reaction of all the starting material. However purification of the reaction product by preparative layer chromatography gave none of the desired product, iheyamine A, but some unidentified compounds were obtained. The ^1H NMR spectra of the unidentified compounds showed only signals in the aliphatic region which indicated the break down of the molecule under these reaction conditions.

Time constrains prevented further investigation of the *N*-demethylation step or the assessment of other *N*-protecting groups.

4.8 Summary and Conclusions

Progress was made towards the synthesis of the marine natural product iheyamine A. A route to the preparation of new spirooxindoles was developed based on condensation of commercially available tryptamine and isatins. These spirooxindoles were then reduced to unstable indolinols, which were then converted to the key bis-indole fused seven membered ring system of the iheyamine skeleton when treated with acid.

5 Antimicrobial Assay

5.1 Introduction

The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Antimicrobial resistance refers to micro-organisms that have developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents.[193] The incidence of antimicrobial resistance has been increasing over the past few decades. Data from the World Health Organization indicated that between 50-90% of microbially caused conditions in India and Sri Lanka are resistant to commonly used antimicrobial drugs.[194] In the US, about 70% of hospital acquired infections were found be resistant.[195] Increasing reports of outbreaks of antimicrobial resistant bacteria have heightened the concerns of the international public and animal health communities, medical and veterinary clinicians and the general public. Despite the use of new antimicrobial agents, the microorganisms have developed mechanisms to overcome the effects of these potent drugs. Experts believe the only solution is to continue to develop new drugs to replace those that are losing their effectiveness.[195]

5.2 Resistance to antibacterial agents

Since the discovery of penicillin G, many new antibiotics have reached the market. However, bacterial resistance occurred only a year after the penicillins were introduced. All strains of the human pathogen *Staphylococcus aureus* (Golden Staph; Figure 5-1) are capable of destroying penicillin by the β-lactamase enzymes. Improvement of the activity spectrum is required to overcome this resistance phenomena. A semi-synthetic penicillin,

named methicillin, has been rendered ineffective due to the emergence of a methicillin-resistant *S. aureus* (MRSA) strain which is a major problem worldwide, especially in hospitals. Vancomycin, the antibacterial drug of last resort, is also losing its effectiveness. In 1986, vancomycin-resistance was reported. Then in 1997, partially vancomycin-resistant strains of *Staphylococcus aureus* were discovered and a few years later the first fully resistant case of vancomycin-resistant *S. aureus* were reported.[196,195,197] The great success in developing new antibacterial drugs, along with the widespread and sometimes inappropriate use of antimicrobials, has resulted in increasing numbers of resistant strains.

Figure 5-1. *Staphylococcus aureus* bacteria (Golden Staph).

Bacterial resistance results from chromosomal mutation, inductive expression of a later chromosomal gene or by exchange of genetic material through transformation, transproduction, or conjugation by plasmids.[198] For example, resistance to quinolones and streptomycin arises from a chromosomal mutation in a single DNA base resulting in the production of proteins that can not bind antibiotics but can still function normally.

5.3 Resistance to antimalarial agents

Malaria is one of the world's most important diseases, killing 1-3 million people and causing disease in 300-500 million people each year.[199] Malaria is caused by the protozoan parasite *Plasmodium*. There are four different species of plasmodium which cause the disease in humans, namely *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* is by far the most dangerous species and can be found throughout tropical Africa, Asia and Latin America. The other species are often found in Central and South America and in some parts of Asia.[200] Malaria is transmitted by the bite of a mosquito carrying the plasmodium parasite. The malarial parasites have a life cycle which is split between a vertebrate host (human) and an insect vector (Anopheles mosquito). When the mosquito bites a human, the parasites enter the human blood circulation and arrive in the liver where they multiply. A few days later, they return to the bloodstream and invade the red blood cells. If disease develops, the parasite density in the blood may obstruct the blood vessels. This may lead to damage to the organ supplied by these blood vessels. The most severe condition is obstruction of small blood vessels in the brain. This is known as cerebral malaria and may cause serious damage or death.

A number of antimalarial drugs have been introduced to combat this disease such as chloroquine, sulphadoxine-pyrimethamine and artermisinin. However, eradication of this disease is difficult since the incidence of this disease is increasing dramatically, mainly due to malaria parasites becoming resistant to antimalarial drugs.[201] Resistance to chloroquine, the most widely used and highly effective drug used to treat malaria, has now emerged in most parts of the world. However, in spite of the prevalence of chloroquine-resistant *P. falciparum*, this drug is still currently used because it is cheap, time tested and a safe

antimalarial agent. Sulphadoxine-pyrimethamine is the other widely used inexpensive antimalarial drug combination but resistance has emerged in many areas in Asia, South America, and Africa.[202]

As malaria is a serious disease and with resistance of the parasite such a problem, the search for new antimalarial drugs (hopefully with new modes of action) has focussed on rapid efficacy, minimal toxicity and low cost. The *in vitro* screening of compounds from natural products, semi-synthetic natural products or synthetic compounds for their antimalarial activity is a critical path for antimalarial drug discovery.

Most antimicrobial agents have been discovered from naturally occurring sources. However, most current antimicrobial drug candidates that are in advanced clinical trials are semi-synthetic derivatives of natural products.[203]

5.4 Antimicrobial assays

Once lead compounds are discovered, one of the key steps in the development of novel drug candidates is the microbiological assay. Antimicrobial assays are used to determine the potentcy or activity of the antimicrobial compounds. Most antimicrobial assay methods[204] use an inoculum of the test organism which is added to a solution of the chemical, then, after a period of time, the proportion of surviving cells is determined. Alternatively, the culture medium is present together with the chemical, then after a period of time, the degree of inhibition of the test organism is measured, compared to that of a reference standard. The minimum inhibitory concentration (MIC), which is the minimun amount of compound required to inhibit the growth of a particular organism, is a fundamental measure of the intrinsic antimicrobial activity (potency) of a compound. IC_{50}

is also commonly used, and is defined as the concentration of chemical at which 50% of the organism growth has been inhibited. The MIC and IC_{50} values are usually expressed in terms of μg/mL or μM.

The indolo-benzodiazocine derivatives synthesised in this project contain a framework (Figure 5-2) incorporating a H, OMe and F in the C-10 position (R in Figure 5-2) and a substituent at N-5 (R′ in Figure 5-2). A number of these compounds were sent for antibacterial testing.

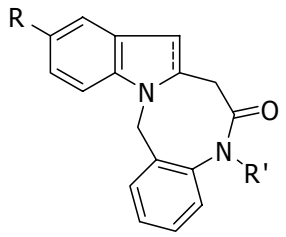


Figure 5-2. The generic indolo-benzodiazocine structure.

The assay was undertaken to determine antibacterial activity against *Staphylococcus aureus* strain ATCC 6538P and VRE strains 243, 449, 820 and 987 (vancomycin-resistant and vancomycin-sensitive *Enterococcus faecium*) at the Avexa (formally Amrad) Corporation laboratories, Melbourne, using the antibacterial screening methodology described in **Appendix 1.1**. All samples were prepared in DMSO (2.5%) solution.

Selected indolo-benzodiazocine derivatives, namely compounds **186d**, **187d** and **186e**, were sent for *in vitro* antimalarial testing against the K1 strain (antifolate resistant strain) and TM4 strain (antifolate sensitive strain) of *Plasmodium falciparum* at the Protein-Ligand Engineering and Biotechnology laboratory, National Science and Technology Development Agency in Bangkok, Thailand. The tests were done by Dr. Sumalee

Kamchonwongpaisan and Miss Roonglawan Rattanajak using a Microdilution Radioisotopes Technique. Details of this method are described in **Appendix 1.3**.

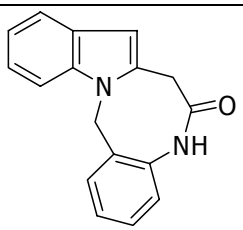
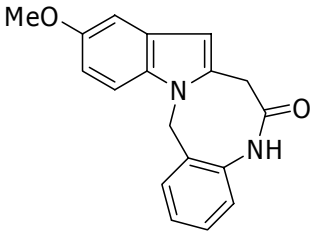
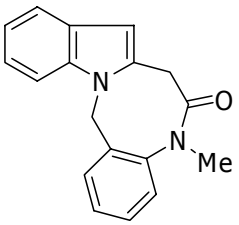
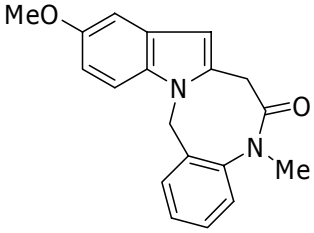
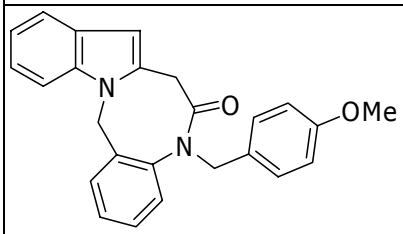
5.5 Results of the antibacterial testing

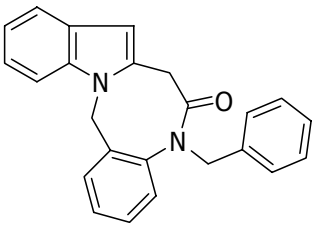
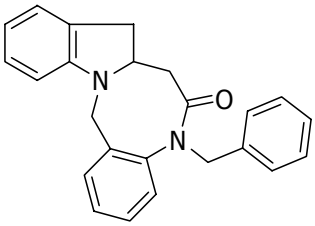
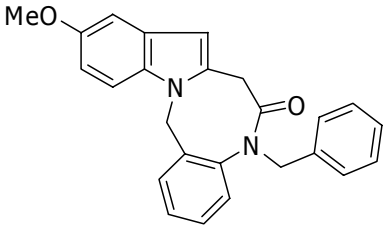
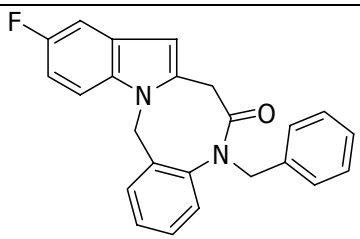
The antibacterial testing results are shown in Table 5-1. The indolo-benzodiazocine derivatives with no substitutent on the nitrogen (N-5) showed no activity against *S. aureus* and vancomycin-resistant and vancomycin sensitive *Enterococcus faecium* (*E. faecium*). The indolo-benzodiazocine derivatives with a methyl, *p*-methoxybenzyl or benzyl substituent at N-5 were also essentially inactive against all strains, with MIC values greater than 125 μg/mL. The same result was also obtained from the testing of 5-benzyl-10-fluoro-indolo-benzodiazocine **186g**, which had MIC values greater than 125 μg/mL against *S. aureus* and the VRE strains. Some antibacterial activity was observed for the 5-substituted-10-methoxy-indolo-benzodiazocines. The 5-methyl derivative **186c** showed good activity against *S. aureus* with an MIC value of 7.8 μg/mL, while the activity against vancomycin-resistant and vancomycin sensitive *E. faecium* was weak with MIC values at 125 μg/mL. However, the 5-benzyl derivative **186f** showed a dramatic drop in activity with an MIC value of 125 μg/mL against *S. aureas* and no activity against the VRE strains. A tetrahydro-indolo-benzodiazocine analogue **187e** was also evaluated for its antibacterial activity. With the 5-benzyl substituent, the activity against *S. aureus* was weak with an MIC value of 125 μg/mL.

From the anitbacterial test results, it is clear that the indolo-benzodiazocine derivative containing a methoxy substituent at the C-10 position exhibited antibacterial activity while the potency depended on the group attached to the amide nitrogen. The size

of the amide substituent might be important to the antibacterial activity. Increasing of the size from a hydrogen to a methyl group also raised the activity markedly, however, when the size was increased to a benzyl group, the activity dropped significantly. Thus, the groups which have a size between methyl and benzyl group would be of interest to test against *S. aureus* and the VRE strains. Furthermore, the compounds containing a methoxy at the 10-position on the tetrahydro-indolo-benzodiazine scaffold would also be of interest as a lead compound for the indole-fused eight-membered ring antibacterial agents.

Table 5-1. Results of antibacterial testing. MIC values in μg/mL.

Compounds		*S.aureus* (MIC)	VRE strains (MIC)			
			243	449	820	987
	**29a**	>125	>125	>125	>125	>125
	**29b**	>125	>125	>125	>125	>125
	**186b**	>125	>125	>125	>125	>125
	**186c**	7.8 (25)	125	125	125	125
	**186d**	>125	>125	>125	>125	>125

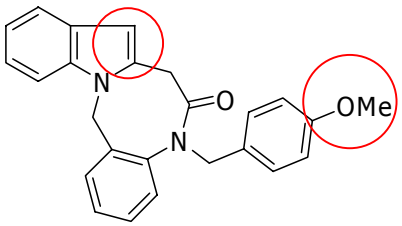
Compounds		*S.aureus* (MIC)	VRE strains (MIC)			
			243	449	820	987
	**186e**	>125	>125	>125	>125	>125
	**187e**	125 (353)	>125	>125	>125	>125
	**186f**	125 (327)	>125	>125	>125	>125
	**186g**	>125	>125	>125	>125	>125
Vancomycin (Standard)		2.5	<9.80, 1.95	62.5	>125	<0.98

MIC-Minimum inhibitory concentration. Values in brackets are µM.

5.6 Results of antimalarial testing

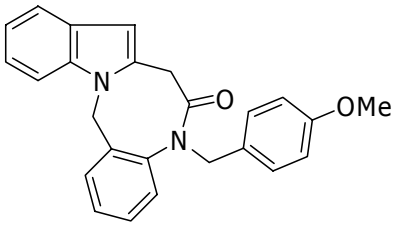
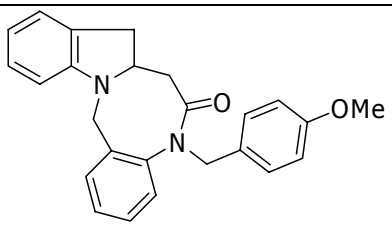
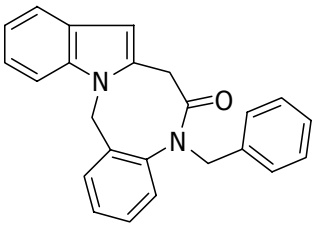
Some indolo-benzodiazocine derivatives were tested against two particular strains (K1 and TM4) of the protozoan *Plasmodium falciparum in vitro*. The results showed that the *p*-methoxybenzyl derivative **186d** had good activity against *P. falciparum* for both the K1 and TM4 strains with IC_{50} values of 4.57 μM and 4.26 μM, respectively. With a benzyl substituent at N-5, compound **186e** showed an activity greater than 10 μM and thus only weakly active against the K1 and TM4 strains of the parasite.

The test against both strains of *P. falciparum* of the 5-*p*-methoxybenzyl-tetrahydro derivative **187d** also showed weak activity, with IC_{50} values for both strains greater than 10 μM. Thus, this suggested that both the *p*-methoxy group in the benzyl group and the double bond of the pyrrole ring are of importance for antimalarial activity. This methoxy group may bind to a hydrophobic region in the biological target or act as a hydrogen acceptor group. While the mechanism of action remains unknown, compound **186d** provides a very interesting, structually different anti-malarial lead compound for further development.



186d

Table 5-2. Results of antimalarial testing.

Compounds		*P. falciparum* (IC_{50}, μM)	
		K1 strain	TM4 strain
	**186d**	4.57±0.41	4.26±0.90
	**187d**	>10	>10
	**186e**	>10	>10

IC_{50} – concentration for 50% inhibition

6 Conclusions and Future Directions

6.1 Conclusions

Successful syntheses of 1,2- and 2,3-fused indoles with seven- or eight-membered rings were developed via thermal free radical cyclisation of iodo- or bromoacetamide precursors. Using 1-substituted indole derivatives with haloacetamide funtionalities, the cyclisation products depended on the protecting group on the haloacetamide nitrogen. When a sufficiently large protecting group (for example a benzyl group) was employed the indole fused eight-membered ring cyclisation products, the indolo-benzodiazocines, were formed. Cyclisation in high boiling point solvents such as xylenes and mesitylene increased the yields of the cyclisation product. The temperature effect was rationalised in terms of the increase in the concentration of the *cisoid* amide rotamer required for cyclisation. A search for alternative means to access the free radical intermediates revealed that although 1-ethylpiperidinium hypophosphite (EPHP) and tris(trimethylsilyl)silane ($(TMS)_3SiH$) could be used, the yields of cyclisation products were lower compared to those from the reaction with tributyltin hydride (Bu_3SnH). Selective deprotection of the benzyl protecting group in one of the 8-membered ring compounds was achieved in 35% yield when reacted with Na in liquid ammonia over a short peroid of time.

Free radical cyclisation of haloacetamide intermediates was also developed for the synthesis of 2,3-fused indoles, in particular the indolo[3,2-*d*][1]benzazepinone (paullone) systems. 2-Substituted indole derivatives with haloacetamide funtionalities were prepared as the key intermediates in this cyclisation. The results obtained in this work showed that both cyclisation to the paullone and/or spiro compound formation occurred in this reaction when using toluene as a solvent. Use of a high boiling point solvent such as mesitylene

increased the yield of the cyclisation product and none of the spiro compound was isolated. This result also supported the idea that increased temperature resulted in an increase in the concentration of the *cisiod* amide rotamer required for cyclisation. Deprotection of the *N*-benzyl protecting group present was also achieved using Na in liquid ammonia, affording access to the *N*-unsubstituted derivative **29a**.

The bis-indole fused seven-membered ring system present in the cytotoxic marine natural product, iheyamine A, was synthesised via a short 3-step route involving the condensation of tryptamine and *N*-substituted isatins. Partial reduction of the *N*-substituted spirooxidoles produced in the first step was successful when using *Red-Al*® in toluene as a reducing agent. The spiro-indolinols obtained from the partial reduction underwent rearrangement to what is believed to be the 12*H*-azepino[3,2-*b*:4,5-*b*´]diindole ring system under acidic conditions, as in the synthesis of **270** and **271**.

Antimicrobial assays of a selection of the new compounds prepared showed that compound **186c**, 5,14-dihydro-10-methoxy-5-methylindolo[2,1-*d*][1,5]benzodiazocin-6-one, exhibited by far the most potent antibacterial property in this series with an MIC of 7.8 μM against the Gram-positive pathogen, *Staphylococcus aureus*, while compound **186d**, 5,14-dihydro-5-(4-methoxybenzyl)indolo[2,1-*d*][1,5]benzodiazocin-6-one, showed good activity against the malarial parasite *Plasmodium falciparum* for the K1 and TM4 strains with IC_{50} values of 4.57 μM and 4.26 μM, respectively. Thus these indole fused eight-membered ring compounds are of interest as new drug leads as both antibacterials and antimalarials.

6.2 Future Directions

Structural verification of the bis-indole fused seven membered ring compounds **270** and **271** should be sought by attempting to obtain suitable crystals for X-ray crystallographic analysis. Preparation of other *N*-substituted spirooxindoles should be investigated with a view to selective removal of the *N*-substituent after rearrangement and completion of the synthesis of the natural product, iheyamine A.

It would also be of interest to synthesise, especially via tin-free radical cyclisation,[205] a number of analogues of the indole fused seven- or eight-membered ring systems with a variety of *N*-substituents (in the 7- or 8-membered ring) and to evaluate their antimicrobial activities. After removal of the *N*-benzyl protecting group, introduction of substituents which have a larger size than methyl group but smaller size than benzyl group on the nitrogen, such as ethyl, propyl, *i*-propyl, allyl and methylcyclopropyl groups, could be investigated and tested for their antimicrobial activity.

7 Experimental

7.1 General procedure

Melting points were determined using a Reichert hot-stage melting point apparatus and are uncorrected.

300 MHz ^{1}H NMR spectra and 75 MHz ^{13}C NMR spectra were recorded on a Varian Mecury 300 Fourier transform NMR spectrometer. 500 MHz ^{1}H NMR spectra and 125 MHz ^{13}C NMR spectra were recorded on a Varain Unity Inova spectrometer. Unless otherwise stated, the spectra were obtained from solutions in $CDCl_3$ and referenced to TMS (proton) and chloroform mid-line (77 ppm) (carbon). Chemical shifts were reported in parts per million (δ). Where an aromatic proton signal appeared as a triplet of doublets (td) in the ^{1}H NMR, the first coupling constant given is for both identical *ortho* couplings.

Low resolution chemical ionisation (CI^{+}) and electron impact (EI) were obtained using a Shimadzu QP-5000 spectrometer. High resolution mass spectra (HRMS) were obtained using a Fisons/VG Autospec-TOF spectrometer.

IR spectra were recorded with a BOMEM MB-100 FTIR using a KBr disc. The UV spectra (solvent corrected) were recorded on a Shimadzu 2401-PC UV-VIS spectrophotometer.

TLC and preparative thin layer chromatography was performed using Merck silica gel 60 F_{254}. All chromatographic solvent proportions are volume for volume. Column chromatography was performed using Merck Kieselgel 60 (0.063-0.200 nm particle size) silica gel.

All solvents used were AR grade, except DCM and hexane, which were distilled prior to use. Tetrahydrofuran (THF) was dried over sodium metal/benzophenone and

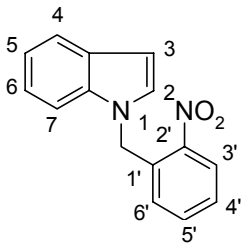
distilled under nitrogen. Solvents were removed under reduced pressure with a rotary evaporator, and organic solvent extracts were dried with anhydrous Na_2SO_4. Solvent mixtures are volume for volume. Petroleum spirit (Pet. spirit) refers to the fraction of b.p. 40-60 °C.

Chemicals were purchased from Sigma-Aldrich Chemical Co. Inc. or Lancaster International and were used as received.

7.2 Experimental for Chapter 2

7.2.1 *N*-alkylation of indoles

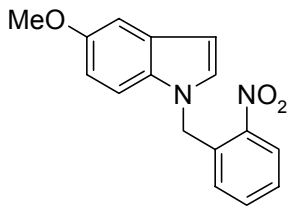
Synthesis of 1-[(2-nitrophenyl)methyl]-1*H*-indole (148a)



A stirred suspension of sodium hydride (*ca* 50% dispersion in mineral oil, 2.6 g, 50 mmol) in dry DMF (50 mL) under a N_2 atmosphere was cooled to 0 ^oC and 1*H*-indole (5.8 g, 54.2 mmol) in DMF solution (150 mL) was added dropwise, with stirring over 30 min. Stirring was continued with cooling for a further 30 min and then at r.t. for 2 h. At this point excess DMF (120 mL) was added to the solution and then cooled to -60 ^oC in a dry ice/acetone bath. To the cold reaction mixture, a solution of 2-nitrobenzyl bromide (13.7 g, 64 mmol) in DMF (50 mL) was added dropwise and the deep red mixture allowed to stir overnight with warming to r.t.. DMF was removed under high vacuum and a mixture of water and ice (400 mL) was added to the residue with vigorous stirring for 4 h. The yellow solid precipitated was suction filtered, washed with cold water and air dried to give the title compound **148a**. Recrystallisation from ethanol gave **148a** (8.5 g, 62%) as yellow crystals; mp 88-90 ^oC (lit.[30] 90.5–92 ^oC); ^1H NMR ($CDCl_3$) δ 5.76 (s, 2H, CH_2), 6.47 (dd, *J*= 9.0, 4.2 Hz, 1H, H-6′), 6.63 (d, *J*=3.0

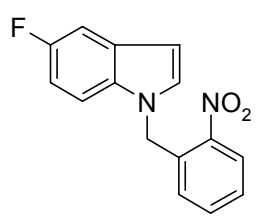
Hz, 1H, H-3), 7.12-7.15 (m, 4H, H-2, H-6, H-5, and H-4′), 7.35-7.41 (m, 2H, H-7 and H-5′), 7.67 (d, *J*= 8.4 Hz, 1H, H-4), 8.16 (dd, *J*= 9.6, 4.5 Hz, 1H, H-3′); CI-MS *m/z* 254 ($[M+H]^+$, 100%).

Synthesis of 5-methoxy-1-[(2-nitrophenyl)methyl]-1*H*-indole (148b)



To a stirred suspension of NaH (*ca* 50% dispersion in mineral oil, 0.70 g, 14.9 mmol) in DMF (20 mL) at 0 ^oC under a N_2 atmosphere was added a solution of 5-methoxyindole (2.0 g, 13.6 mmol) in DMF (50 mL) dropwise. The suspension was stirred at 0 °C for 30 min and then at r.t. for 2 h. DMF (150 mL) was added and then the mixture cooled to -60 ^oC using a dry ice/acetone bath. A solution of 2-nitrobenzyl bromide (3.8 g, 17.4 mmol) in DMF (25 mL) was added dropwise and the mixture was allowed to stir overnight at r.t.. DMF was then removed under reduced pressure until the mixture was almost free of solvent. Ice water was then added to the residue with vigorous stirring. The solid was filtered through filter paper, washed with cold water and air dried. The solid was crystallised from ethanol to give **148b** (2.45 g, 63%) as yellow crystals; mp 120-121 ^oC (lit. [30] 117-119 ^oC); ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H, OCH_3), 5.72 (s, 2H, CH_2), 6.45 (d, *J*= 9.0 Hz, 1H, H-6′), 6.57 (d, *J*= 3.0 Hz, 1H, H-3), 6.80 (dd, *J*= 9.3, 2.4 Hz, 1H, Ar), 7.00 (d, *J*= 9.0 Hz, 1H, Ar), 7.11-7.21 (m, 2H, H-2 and Ar), 7-35-7.44 (m, 2H, Ar), 8.16 (d, *J*= 9.3 Hz, 1H, H-3′); CI-MS *m/z* 284 ($[M+H]^+$, 100%).

Synthesis of 5-fluoro-1-[(2-nitrophenyl)methyl]-1*H*-indole (148c)

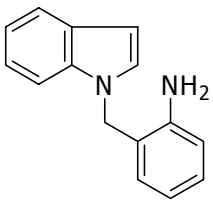


To a stirred suspension of NaH (*ca* 50% dispersion in mineral oil, 1.2 g, 24.4 mmol) in DMF (50 mL) at 0 ^oC under a N_2 atmosphere was added a solution of 5-fluoroindole (3.0 g, 22.2 mmol) in DMF

(50 mL) dropwise. The suspension was stirred at 0 °C for 30 min and then at r.t. for 2 h. DMF (150 mL) was added and then the mixture cooled to -60°C using a dry ice/acetone bath. A solution of 2-nitrobenzyl bromide (6.1 g, 28.4 mmol) in DMF (25 mL) was added dropwise and the mixture was allowed to stir overnight at r.t.. DMF was then removed under reduced pressure until the mixture was almost free of solvent. Ice water was then added to the residue with vigorous stirring. The solid was filtered through filter paper, washed with cold water and air dried. The solid was crystallised from ethanol to give **148c** (3.76 g, 63%) as yellow crystals; mp 114-115 °C (lit.[30] 118-119 °C); ^{1}H NMR ($CDCl_3$) δ 5.73 (s, 2H, CH_2), 6.44 (dd, *J*= 5.7, 3.3 Hz, 1H, H-6′), 6.57 (d, *J*= 3.0 Hz, 1H, H-3), 6.90 (td, *J*= 9.0, 2.4 Hz, 1H, Ar), 7.03 (dd, *J*= 8.7, 4.2 Hz, 1H, H-7), 7.16 (d, *J*= 3.0 Hz, 1H, H-2), 7.29 (dd, *J*= 9.6, 2.4 Hz, 1H, Ar), 7.39-7.44 (m, 2H, Ar), 8.15 (d, *J*= 9.3 Hz, 1H, H-3′); CI-MS *m/z* 271 ($[M+H]^+$, 100%).

7.2.2 Reduction procedure

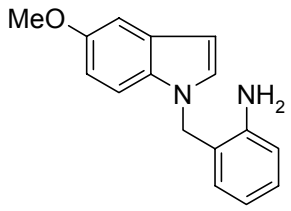
Synthesis of 1-[(2-aminophenyl)methyl]-1*H*-indole (149a)



A solution of **148a** (4.15 g, 16.5 mmol), 10% Pd/C (1 g), and 2 drops of conc. HCl in THF (100 mL) was stirred under a H_2 atmosphere at r.t. overnight. The catalyst was removed by filtration, washed with DCM (5 x 10 mL), and the filtrate dried and evaporated to give an orange oil. The oil was taken up in a minimal volume of hot ethanol and the crystals obtained on cooling were suction filtered to yield the title compound **149a** (1.85 g, 50%) as a tan crystalline solid; mp 76-77 °C (lit.[30] 79-80.5 °C); ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 2H, NH_2), 5.16 (s, 2H, CH_2), 6.52 (d, *J*= 3.0 Hz, 1H, H-3), 6.67 (d, *J*= 7.8 Hz, 1H, H-3′), 6.70 (t, *J*= 7.2 Hz, 1H, Ar), 6.99 (d, *J*= 8.1 Hz, 1H, Ar), 7.01 (d, *J*= 2.7 Hz, 1H, H-2), 7.08-7.23 (m,

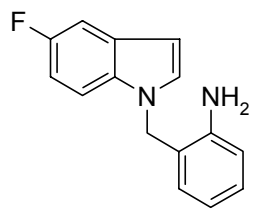
3H, H-5, H-6, and Ar), 7.39 (d, *J*=8.1 Hz, 1H, H-7), 7.65 (d, *J*=7.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 47.9 (CH_2), 102.3 (C-3), 109.8 (C-7), 116.6, 119.2, 120.0, 121.3, 121.3, 122.0, 127.5 (all ArC-H), 129.1 (C-3a), 129.5 (ArC-H), 130.0 (ArC-H), 136.5 (C-7a), 145.1 (C-N); CI-MS *m/z* 223 ($[M+H]^+$, 100%).

Synthesis of 1-[(2-aminophenyl)methyl]-5-methoxy-1*H*-indole (149b)



A solution of **148b** (2.39 g, 8.5 mmol), 10% Pd/C (1 g), and 2 drops of conc. HCl in THF (100 ml) was stirred under a H_2 atmosphere at r.t. overnight. The catalyst was removed by filtration, washed with DCM (5 x 10 mL), and the filtrate dried and evaporated to give an orange oil. The oil was subjected to flash column chromatography (silica gel, DCM) to give **149b** (1.19 g, 56%) as a tan crystalline solid; mp 121- 124 ^{o}C (lit.[30] 118-120 ^{o}C); ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 2H, NH_2), 3.87 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 6.47 (dd, *J*= 3.3, 0.6 Hz, 1H, H-3), 6.69 (dd, *J*= 7.8, 0.9 Hz, 1H, H-3′), 6.79 (td, *J*= 7.2, 0.9 Hz, 1H, H-5′), 6.88 (dd, *J*= 8.7, 2.4 Hz, 1H, H-6), 6.91-7.01 (m, with prominent d, *J*= 3.3 Hz, 2H, H-2 and H-6′), 7.13 (d, *J*= 2.4 Hz, 1H, H-4), 7.17 (td, *J*= 7.8, 1.5 Hz, 1H, H-4′), 7.28 (d, *J*= 8.7 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 48.1 (CH_2), 56.2 (CH_3), 101.8 (C-4), 103.0 (C-3), 110.5 (C-6), 112.3 (C-7), 116.6 (C-3′), 119.2 (C-5′), 121.4 (C-1′), 128.1 (C-2), 129.4 (C-3a and C-4′), 129.9 (C-6′), 131.9 (C-7a), 145.1 (C-N), 154.4 (*C*OCH_3); CI-MS *m/z* 253 ($[MH]^+$, 100%).

Synthesis of 1-[(2-aminophenyl)methyl]-5-fluoro-1*H*-indole (149c)



A solution of **148c** (3.24 g, 12 mmol), 10% Pd/C (1 g), and 2 drops of conc. HCl in THF (100 ml) was stirred under a H_2 atmosphere at r.t. overnight. The catalyst was removed by filtration, washed with DCM (5 x 10 mL), and the filtrate dried

and evaporated to give an orange oil. The oil was subjected to flash column chromatography (silica gel, DCM) to give **149c** (1.30 g, 45%) as yellow crystalline solid; mp 81-82 ^{o}C (lit.[30] 81.0-82.5 ^{o}C); ^{1}H-NMR ($CDCl_3$) δ 3.48 (br.s, 2H, NH_2), 5.15 (s, 2H, CH_2), 6.48 (d, *J*= 3.2 Hz, 1H, H-3), 6.70 (d, *J*= 8.1 Hz, 1H, Ar), 6.77 (ddd, *J*= 7.6, 7.3, 1.0 Hz, 1H, Ar), 6.86-7.00 (m, 2H, Ar), 7.06 (d, *J*= 3.2 Hz, 1H, H-2), 7.17 (ddd, *J*= 7.8, 7.6, 1.2 Hz, 1H, Ar), 7.23-7.31 (m, 2H, Ar); ^{13}C-NMR ($CDCl_3$) δ 48.2 (CH_2), 102.1 (C-7), 102.2 (C-3), 105.9 (ArC-H), 106.2 (C-6), 110.2, 110.3, 110.4, 110.6, 116.7 (all ArC-H), 119.3 (ArC-H), 121.0 (C-3a), 129.1, 129.6, 129.9 (ArC-H), 133.2 (C-7a), 145.0 (C-N); CI-MS *m/z* 241 ($[MH]^+$, 100%)

7.2.3 *N*-methylation of primary amines

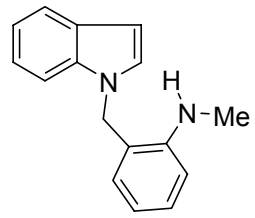
N-Methylation of 149a

Method A: To a stirred solution of **149a** (0.15 g, 0.71 mmol) in dry DMF (20 mL) under a N_2 atmosphere was added anhydrous K_2CO_3 (98 mg, 0.71 mmol) and the suspension was stirred at 0-5 ^{o}C for 5 min. Methyl iodide (48 μL, 0.78 mmol) was then added and the reaction mixture stirred at r.t. overnight. Solvent was then removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and concentrated to give a brown oil. ^{1}H NMR of the oil confirmed the formation of **150a** with the starting material **149a** also present. The oil was purified by flash column chromatography (1:1 hexane/DCM) to give the first fraction as 1-[(2-*N*-methylaminophenyl)methyl]-1*H*-indole **150a** (51 mg, 31%) and the second fraction as starting material **149a** (77 mg, 48%).

Method B: A suspension of **149a** (0.16 g, 0.71 mmol), anhydrous K_2CO_3 (98 mg, 0.71 mmol) and methyl iodide (66 μL, 1.07 mmol) was treated as described above in method

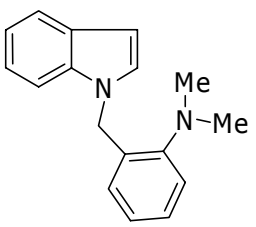
A. The crude product was purified by column chromatography (1:1 hexane/DCM). The first fraction gave 1-[(2-*N*,*N*-dimethylaminophenyl)methyl]-1*H*-indole **151a** (48 mg, 27%), the second fraction gave **150a** (70 mg, 42%) and the third fraction gave the starting material **149a** (25 mg, 16%).

Method C: A suspension of **149a** (0.30 g, 1.40 mmol), anhydrous K_2CO_3 (0.20 g, 1.40 mmol) and methyl iodide (18 μL, 0.28 mmol) was treated as described above in method A. The crude product was purified by column chromatography (1:1 hexane/DCM). The first fraction gave **150a** (80 mg, 90%), while the second fraction gave the starting material **149a** (0.24 g, 79%).



150a

150a was obtained as a colourless solid; mp 52-53 ^{o}C; IR (KBr) ν_{max}: 3430 (NH), 2815 (N-CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H, CH_3), 3.51 (br.s, 1H, NH), 5.15 (s, 2H, CH_2), 6.53 (d, *J*= 3.6 Hz, 1H, H-3), 6.70 (d, *J*= 8.1 Hz, 1H, H-3′), 6.75 (d, *J*= 7.5 Hz, 1H, Ar), 6.99 (m, *J*= 8.4 Hz, 2H, H-2 and Ar), 7.13-7.33 (m, 3H, H-2′, H-5 and H-6), 7.42 (d, *J*= 8.1 Hz, 1H,H-7), 7.67 (d, *J*= 7.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 31.0 (CH_3), 47.7 (CH_2), 102.2 (C-3), 109.7 (C-7), 110.6 (x2), 117.5, 120.0, 121.1 (C-1′), 121.3, 122.0, 127.4 (all ArCH), 129.8 (C-3a and ArCH), 136.5 (C-7a), 147.5 (C-2′); CI-MS *m/z* 237 ($[MH]^+$, 97%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{16}N_2$: 236.1313, found: 236.1309.



151a

151a was obtained as a brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 (s, 6H, 2xCH_3), 5.44 (s, 2H, CH_2), 6.51 (d, *J*= 8.0 Hz, 1H, H-3′), 6.56 (d, *J*= 3.0 Hz, 1H, H-3), 6.67 (t, *J*= 7.5 Hz, 1H, Ar), 6.72 (d, *J*= 8.5 Hz, 1H, Ar), 6.91 (td, *J*= 7.5, 2.0 Hz, 1H, Ar), 7.04-7.27 (m, 3H, Ar), 7.45 (d, *J*= 7.0 Hz, 1H, H-7), 7.66 (d, *J*= 7.0 Hz, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.2 (NCH_3), 45.4 (CH_2), 101.6 (C-3), 107.0 (C-

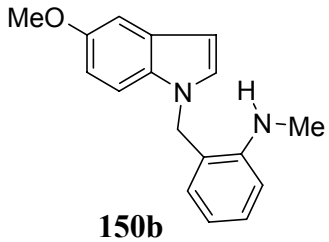
7), 110.1, 117.5, 119.4, 119.6, 121.1, 121.4 (C-1′), 123.3, 127.5, 128.4, 128.7 (C-3a), 129.3 (ArCH), 132.8 (C-7a), 152.9 (C-2′); EI-MS *m/z* 250 ($[M]^+$, 54%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{18}N_2$: 250.1470, found: 250.1461.

_N_-Methylation of 149b

Method A: To a solution of **149b** (0.39 g, 1.54 mmol) in dry DMF (40 mL) under a N_2 atmosphere was added anhydrous K_2CO_3 (0.21 g, 1.54 mmol) and the suspension was stirred at 0-5 ^oC for 5 min. Methyl iodide (0.1 mL, 1.69 mmol) was then added and the reaction mixture stirred at r.t. overnight. Solvent was then removed under reduced pressure. Diethyl ether (30 mL) was added to the residue and the mixture was washed with water (5 x 25 mL). The organic layer was dried and concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent. The first fraction gave 1-[(2-*N*-methylaminophenyl)methyl]-5-methoxy-1*H*-indole **150b** (0.29 g, 71%) and the second fraction gave the starting material **149b** together with some contaminants (0.15g , 36%).

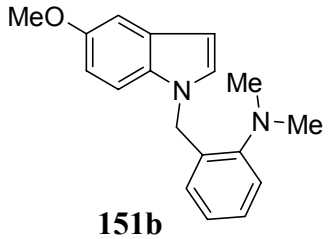
Method B: A suspension of **149b** (0.54 g, 2.14 mmol), anhydrous K_2CO_3 (0.30 g, 2.14 mmol) and methyl iodide (2.0 mL, 3.21 mmol) was treated as described above in method A. The crude product was purified by column chromatography (DCM). The first fraction gave 1-[(2-*N*,*N*-dimethylaminophenyl)methyl]-5-methoxy-1*H*-indole **151b** (0.14 g, 23%), the second fraction gave **150b** (0.11 g, 19%) and the third fraction gave the starting material **149b** (0.20g, 37%).

Method C: A suspension of **149b** (0.59 g, 2.34 mmol), anhydrous K_2CO_3 (0.32 g, 2.34 mmol) and methyl iodide (30 μL, 0.47 mmol) was treated as described above in method A. The crude product was purified by column chromatography (DCM). The first fraction gave **150b** (50 mg, 40%) and while the second fraction gave the starting material **149b** (0.39 g, 66%).



150b

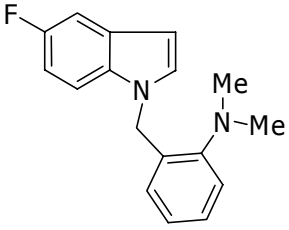
150b was obtained as a yellow solid; mp 59-60 ^{o}C; IR (KBr) ν_{max}: 3429 (NH), 2815 (N-CH_3) cm^{-1}; ^{1}H NMR δ 2.74 (s, 3H, CH_3), 3.48 (br s, 1H, NH), 3.84 (s, 3H, OCH_3), 5.06 (s, 2H, CH_2), 6.42 (d, *J*= 3.6 Hz, 1H, H-3), 6.66-6.73 (m, 2H, Ar), 6.86 (dd, *J*= 8.6, 2.1 Hz, 1H, H-7), 6.92-6.94 (m with prominent d, *J*= 3.3 Hz, 2H, H-2 and Ar), 7.11 (d, *J*= 2.1 Hz, 1H, H-4), 7.22-7.30 (m, 2H, Ar); ^{13}C NMR δ 31.0 (CH_3), 48.1 (CH_2), 56.2 (OCH_3), 101.8 (C-4), 102.9 (C-3), 110.5, 110.6, 112.3, 117.6, 120.7 (C-1′), 128.2 (C-2), 129.5 (C-3a), 129.7, 131.9 (C-7a), 147.5 (C-N), 154.4 (*C*OCH_3); CI-MS *m/z* 267 ([MH]$^{+}$, 100%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{17}H_{18}N_2O$: 267.1497, found: 267.1490.



151b

151b was obtained as a brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (s, 6H, 2xCH_3), 3.85 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2), 6.47 (d, *J*= 3.0 Hz, 1H, H-3), 6.70 (d, *J*= 7.5 Hz, 1H, H-3′), 6.82 (dd, *J*= 9.0, 2.5 Hz, 1H, H-6), 6.92 (td, *J*= 7.5, 1.5 Hz, 1H, Ar), 7.11-7.15 (m, 3H, H-2, H-4 and Ar), 7.18 (dd, *J*= 8.5, 1.5 Hz, 1H, H-6′), 7.22 (d, *J*= 7.5 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4 (NCH_3), 48.0 (CH_2), 55.9 (OCH_3), 102.0 (C-4), 102.7 (C-3), 109.7, 112.0, 114.3, 119.6, 121.0 (C-1′), 123.9, 124.5, 128.1, 129.3 (C-3a), 130.1, 132.4 (C-7a), 147.5 (C-2′), 155.8 (*C*OCH_3); EI-MS *m/z* 280 ([M]$^{+}$, 47%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{18}H_{20}N_2O$: 280.1576, found: 280.1582.

Synthesis of 5-fluoro-1-[(2-*N*,*N*-dimethylaminophenyl)methyl]- 1*H*-indole (151c)

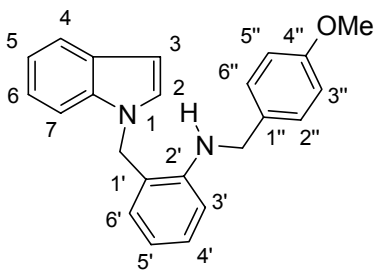


To a solution of **149c** (0.14 g, 0.60 mmol) in dry DMF (5 mL) under a N_2 atmosphere was added anhydrous K_2CO_3 (83 mg, 0.60 mmol) and the suspension was stirred at 0-5 ^{o}C for

5 min. Methyl iodide (41 μL, 0.66 mmol) was then added and the reaction mixture stirred at r.t. overnight. The solvent was then removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and concentrated to give a yellow oil. The oil was subjected to flash column chromatography (DCM) to afford **151c** (0.16 g, 100%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (s, 6H, 2xCH_3), 5.31 (s, 2H, CH_2), 6.44 (d, *J*= 3.0 Hz, 1H, H-3), 6.65 (d, *J*= 7.5 Hz, 1H, H-3′), 6.82-6.86 (m, 2H, Ar), 7.09 (dd, *J*= 9.0, 4.5 Hz, 1H, H-7), 7.12-7.13 (m, 2H, Ar), 7.17 (t, *J*= 7.5 Hz, 1H, H-4′), 7.24 (dd, *J*= 10.0, 2.5 Hz, 1H, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) 45.0 (NCH_3), 45.9 (CH_2), 101.2 (d, *J*= 4.8 Hz, ^{13}C-^{19}F, C3-F), 105.4 (d, *J*= 22.9 Hz, ^{13}C-^{19}F, C4-F), 109.8 (d, *J*= 26.3 Hz, ^{13}C-^{19}F, C6-F), 110.4 (d, *J*= 9.5 Hz, ^{13}C-^{19}F, C7-F), 119.5, 123.6, 127.7, 128.3 (all ArC-H), 128.7 (d, *J*= 10.1 Hz, ^{13}C-^{19}F, C3a-F), 130.1 (ArC-H), 131.8 (C-1′), 133.0 (C-7a), 152.0 (C-2′), 157.8 (d, *J*= 232.8 Hz, ^{13}C-^{19}F, C5-F); EI-MS *m/z* 268 ([M]$^{+}$, 33%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{17}H_{17}N_2F$: 268.1376, found: 268.1375.

7.2.4 *N*-benzylation of primary amines

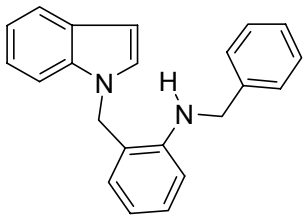
Synthesis of 1-{[2-*N*-(4-methoxybenzyl)aminophenyl]methyl}-1*H*-indole (152)



To a solution of **149a** (0.13 g, 0.59 mmol) in dry DMF (20 mL) was added anhydrous K_2CO_3 (82 mg, 0.59 mmol) and the suspension was stirred at 0-5 ^{o}C for 5 min. 4-Methoxybenzyl bromide (0.12 g, 0.59 mmol) in DMF (2 mL) was then added and the reaction mixture stirred at r.t. overnight. Solvent was then removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and concentrated. The crude material was chromatographed on a silica gel column

using DCM as eluting solvent to give **152** (0.14 g, 71%) as a yellow solid; mp 105-106 ^{o}C; IR (KBr) ν_{max}: 3425 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (br s, 1H, NH), 3.88 (s, 3H, CH_3), 4.26 (s, 2H, NHC*H*$_2$), 5.26 (s, 2H, CH_2), 6.63 (d, *J*= 3.3 Hz, 1H, H-3), 6.77-6.83 (m, 2H, Ar), 6.87 (d, *J*= 8.7 Hz, 2H, Ar), 7.22-7.26 (m, 6H, Ar), 7.32 (t, *J*= 9.0 Hz, 1H, Ar), 7.43 (dd, *J*= 7.5, 1.2 Hz, 1H, H-7), 7.76 (dd, *J*= 7.5, 1.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 47.4 ($NHCH_2$), 47.7 (CH_2), 55.3 (CH_3), 102.0 (C-3), 109.3, 111.2, 113.8, 117.3, 119.6 (all ArC-H), 120.6 (C-1′), 121.0, 121.7, 127.2, 128.3 (all ArC-H), 128.7, (C-3a), 129.2 (ArC-H), 129.4 (ArC-H), 130.6 (C-7a), 136.2 (C-1′′), 146.0 (C-2′), 158.5 (*C*OCH_3); CI-MS *m/z* 343 ($[MH]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{22}N_2O$: 342.1732, found: 342.1731.

Synthesis of 1-[(2-*N*-benzylaminophenyl)methyl]-1*H*-indole (153)

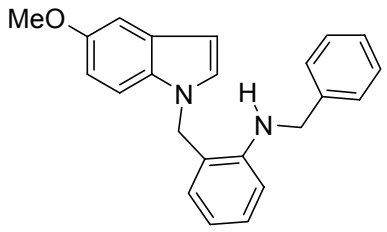


Method A: To a solution of **149a** (0.10 g, 0.45 mmol) in dry DMF (20 mL) was added anhydrous K_2CO_3 (62 mg, 0.45 mmol) and the suspension was stirred at 0-5 ^{o}C for 5 min. Benzyl bromide (53 μL, 0.45 mmol) in DMF (2 mL) was then added and the reaction mixture stirred at r.t. overnight. Solvent was then removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent to give **153** (0.095 g, 67%) as a yellow solid.

Method B: To a solution of **149a** (0.30 g, 1.35 mmol) in absolute methanol (10 mL) with molecular sieves (3Å) was added 5 M HCl-MeOH (90 μL, 0.45 mmol), followed by benzaldehyde (0.14 mL, 1.35 mmol) and $NaBH_3CN$ (85 mg, 1.35 mmol). The reaction mixture was stirred at r.t. for 20 h. The mixture was filtered and the filtrate was evaporated to dryness. Water (20 mL) was added and extracted with DCM (20 mL). The

aqueous layer was brought to pH > 10 with solid KOH and extracted with DCM (3 x 20 mL). The organic extracts were combined and washed with brine (20 mL), dried and concentrated to give a brown oil. The oil was subjected to flash column chromatography by elution with 1:1 DCM/hexane to give compound **153** (0.28 g, 66%) as a yellow solid; mp 89-91 ^{o}C; IR (KBr) ν_{max}: 3432 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.93 (br s, 1H, NH), 4.32 (s, 2H, NHC*H*$_2$), 5.20 (s, 2H, CH_2), 6.65 (dd, *J*= 3.3, 0.6 Hz, 1H, H-3), 6.76 (d, *J*= 8.1 Hz, 1H, H-3′), 6.83 (td, *J*= 7.5, 1.2 Hz, 1H, Ar), 7.07- 7.11 (m, with prominent of d, *J*= 3.3 Hz, 2H, H-2 and Ar), 7.18- 7.38 (m, 8H, Ar), 7.44 (dd, *J*= 7.2, 1.5 Hz, 1H, H-7), 7.78 (dd, *J*= 7.5, 0.9 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 48.0 ($NHCH_2$), 48.3 (CH_2), 102.5 (C-3), 109.8, 111.7, 120.1 (all ArC-H), 121.0 (C-1′), 121.5, 122.2, 127.4, 127.6, 128.9 (all ArC-H), 129.2 (C-3a), 129.7 (ArC-H), 129.8 (ArC-H), 136.6 (C-7a), 139.1 (C-1′′), 146.3 (C-2′); CI-MS *m/z* 313 ([MH]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$ $C_{22}H_{20}N_2$: 312.1625, found: 312.1621.

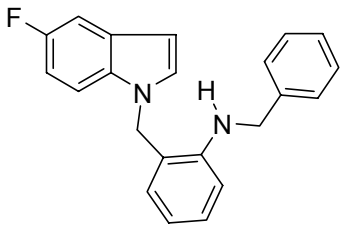
Synthesis of 1-[(2-*N*-benzylaminophenyl)methyl]-5-methoxy-1*H*-indole (154)



Method A: To a solution of **149b** (1.00 g, 4.00 mmol) in dry DMF (50 mL) was added anhydrous K_2CO_3 (0.58 g, 4.17 mmol) and the suspension was stirred at 0-5 ^{o}C for 5 min. Benzyl bromide (0.50 mL, 4.17 mmol) in DMF (10 mL) was then added and the reaction mixture stirred at r.t. overnight. The solvent was then removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent to give **154** (0.80 g, 58%) as a yellow solid.

Method B: To a solution of **149b** (1.05 g, 4.17 mmol) in absolute methanol (30 mL) with molecular sieves (3Å) was added 5 M HCl-MeOH (0.42 mL, 2.09 mmol), followed by benzaldehyde (0.42 mL, 4.17 mmol) and $NaBH_3CN$ (0.26 g, 4.17 mmol). The reaction mixture was filtered and the filtrate was evaporated to dryness. Water (20 mL) was added and extracted with DCM (20 mL). The aqueous layer was brought to pH > 10 with solid KOH and extracted with DCM (3 x 20 mL). The organic extracts were combined and washed with brine (20 mL), dried and concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent to give compound **154** (0.40 g, 28%) as a yellow solid; mp 108-110 ^oC; IR (KBr) ν_{max}: 3428 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H, OCH_3), 4.23 (s, 2H, NHCH_2), 5.17 (s, 2H, CH_2), 6.48 (d, *J*= 3.3 Hz, 1H, H-3), 6.65 (d, *J*= 8.4 Hz, 1H, H-3′), 6.73 (t, *J*= 7.5 Hz, 1H, Ar), 6.81 (dd, *J*= 8.7, 2.4 Hz, 1H, H-6), 6.98- 7.02 (m, 2H, H-2 and Ar), 7.07-7.11 (m, 3H, Ar), 7.18-7.30 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 48.1 (NCH_2), 48.2 (CH_2), 56.1 (CH_3), 101.9 (C-3), 103.0 (C-4), 110.4, 111.6, 112.2, 117.7, 120.8 (C-1′), 127.4, 128.1, 128.8, 129.6, 129.8, 131.8 (C-7a), 139.0 (C-1′′), 146.2 (C-2′), 154.4 (*C*OCH_3); CI-MS *m/z* 343 ($[MH]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{22}N_2O$: 342.1732, found: 342.1731.

Synthesis of 1-[(2-*N*-benzylaminophenyl)methyl]- 5-fluoro-1*H*-indole (155)

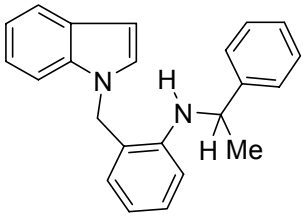


Method A: To a solution of **149c** (1.00 g, 4.12 mmol) in dry DMF (50 mL) was added anhydrous K_2CO_3 (0.57 g, 4.12 mmol) and the suspension was stirred at 0-5 ^oC for 5 min. Benzyl bromide (0.49 mL, 4.12 mmol) in DMF (10 mL) was then added and the reaction mixture stirred at r.t. overnight. The solvent then was removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the mixture was washed with water (5 x 20 mL). The organic layer was dried and

concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent to give **155** (0.65 g, 48 %) as a yellow solid.

Method B: To a solution of **149c** (1.04 g, 4.33 mmol) in absolute methanol (30 mL) with molecular sieves (3Å) was added 5 M HCl-MeOH (0.43 mL, 2.17 mmol), followed by benzaldehyde (0.44 mL, 4.33 mmol) and $NaBH_3CN$ (0.27 g, 4.33 mmol). The reaction mixture was filtered and the filtrate was evaporated to dryness. Water (20 mL) was added and extracted with DCM (20 mL). The aqueous extracts was brought to pH > 10 with solid KOH and extracted with DCM (3 x 20 mL). The organic layers were combined and washed with brine (20 mL), dried and concentrated. The crude material was chromatographed on a silica gel column using DCM as eluting solvent to give compound **155** (0.30 g, 21%) as colourless needles; mp 189-191 ^{o}C; IR (KBr) ν_{max}: 3430 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 2H, NHC*H*$_2$), 5.19 (s, 2H, CH_2), 6.50 (d, *J*= 3.3 Hz, 1H, H-3), 6.71 (d, *J*= 8.1 Hz, 1H, Ar), 6.77 (t, *J*= 7.5 Hz, 1H, Ar), 6.90 (td, *J*= 9.0, 2.7 Hz, 1H, H-6), 7.00 (dd, *J*= 7.5, 1.5 Hz, 1H, Ar), 7.05-7.10 (m with prominent d, *J*= 3.3 Hz, 2H, H-2 and Ar), 7.16-7.27 (m, 6H, Ar), 7.30 (dd, *J*= 9.6, 2.4 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 48.2 ($NHCH_2$), 48.3 (CH_2), 102.3 (d, *J*= 4.9 Hz, ^{13}C-^{19}F, C3-F), 106.1 (d, *J*= 23.2 Hz, ^{13}C-^{19}F, C6-F), 110.9 (d, *J*= 10.3 Hz, ^{13}C-^{19}F, C7-F), 110.8 (d, *J*= 27.8 Hz, ^{13}C-^{19}F, C4-F), 117.0 (ArC-H), 118.1 (ArC-H), 120.9 (C-1′), 127.5, 128.8, 129.15, 129.23 (all ArC-H), 129.5 (d, *J*= 16.3 Hz, ^{13}C-^{19}F, C3a-F), 129.8 (ArC-H), 133.1 (C-7a), 138.6 (C-1′′), 146.0 (C-2′), 158.2 (d, *J*= 233.1 Hz, ^{13}C-^{19}F, C5-F); CI-MS *m/z* 331 ($[MH]^+$, 100%); HREI-MS *m/z* calcd for $C_{22}H_{19}N_2F$: 330.1532, found: 330.1533.

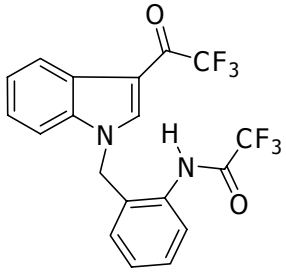
Synthesis of 1-{[2-*N*-(1-phenylethyl)aminophenyl]methyl}-1*H*-indole (156)



To a solution of **149a** (0.30 g, 1.42 mmol) in absolute methanol (10 mL) with molecular sieves (3Å) was added 5 M HCl-MeOH (0.10 mL, 0.50 mmol), followed by acetophenone (40 μL, 0.34 mmol) and $NaBH_3CN$ (10 mg, 0.14 mmol). The reaction mixture was filtered and the filtrate was evaporated to dryness. Water (15 mL) was added and extracted with DCM (15 mL). The aqueous layer was brought to pH > 10 with solid KOH and extracted with DCM (3 x 15mL). The organic extracts were combined and washed with brine (15 mL), dried and concentrated. The crude material was chromatographed on a silica gel column using 1:1 hexane/DCM as eluting solvent to give compound **156** (82 mg, 74 %) as an off-white solid; mp 86-88 ^oC; IR (KBr) ν_{max}: 3425 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, 3H, *J*= 6.6 Hz, CH_3), 3.47 (br s, 1H, NH), 4.33 (q, *J*= 6.6 Hz, 1H, CH), 5.20 (s, 2H, CH_2), 6.37 (d, *J*= 8.1 Hz, 1H, H-3′), 6.57 (d, *J*= 3.3 Hz, 1H, H-3), 6.64 (t, *J*= 7.5 Hz, 1H, H-5′), 6.93-6.95 (m, 2H, H-2′′ and H-6′′), 7.00- 7.10 (m, 3H, H-2, H-4′ and H-6′), 7.11-7.23 (m, 5H, H-5, H-6, H-3′′, H-4′′ and H-5′′), 7.42 (d, *J*= 8.1 Hz, 1H, H-7), 7.66 (d, *J*= 7.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 25.4 (CH_3), 48.6 (CH_2), 53.2 (CH), 102.7 (C-3), 109.7 (C-7), 112.6 (C-6), 117.4 (C-4), 120.1 (C-5), 120.8 (C-1′), 121.6, 122.2, 125.8, 127.1, 127.6, 128.8 (all ArC-H), 129.1 (C-3a), 129.6 (ArC-H), 130.1 (ArC-H), 136.6 (C-7a), 144.9 (C-1′′), 145.8 (C-2′); CI-MS *m/z* 327 ($[MH]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{23}H_{23}N_2$: 327.1861, found: 327.1850.

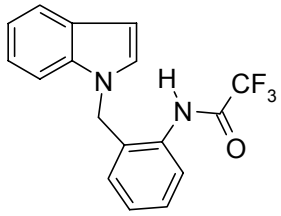
7.2.5 Acylation procedure

Synthesis of *N*-{2-[1-(3-trifluoroacetyl-1*H*-indolyl)methyl]phenyl}trifluoro acetamide (157)



To a stirred solution of **149a** (0.2 g, 0.90 mmol) and pyridine (0.10 mL, 1.35 mmol) in dry DCM (5 mL) was added a solution of trifluoroacetic anhydride (0.19 mL, 1.35 mmol) in DCM (5 mL). The reaction mixture was stirred at r.t. for 4 h and then water (20 mL) was added. The organic layer was separated, dried and concentrated to dryness. The residue was subjected to a short column (silica gel; DCM) to give compound **157** (0.24 g, 67%) as a white solid; mp 177-178 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2H, CH_2), 6.96 (d, *J*= 7.5 Hz, 1H, H-3′), 7.21-7.43 (m, 6H, Ar), 7.93 (s, 1H, H-2), 8.04 (br s, 1H, NH), 8.37 (d, *J*= 7.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 48.4 (CH_2), 110.5 (C-3), 110.8 (C-7), 117.1 (d, *J*= 285 Hz, CF_3), 123.0 (C-4), 124.5 (C-5′), 125.3 (C-6), 126.8 (C-5), 127.2 (C-3a), 128.6 (C-4′), 129.4 (C-3′), 129.9 (C-6′), 131.3 (C-1′), 131.5 (C-2′), 136.9 (C-7a), 137.9 (d, *J*= 7.5 Hz, ^{13}C-^{19}F, C2-F), 156.4 (d, *J*= 45 Hz, ^{13}C-^{19}F, CO-F), 157.3 (d, *J*= 52 Hz, ^{13}C-^{19}F, CO-F); CI-MS *m/z* 414 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{19}H_{12}N_2O_2F_6$: 414.0803, found: 414.0780.

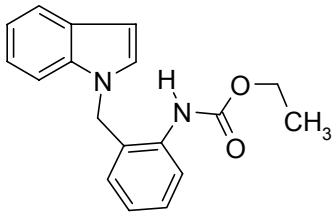
Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}trifluoroacetamide (158)



To a stirred solution of **149a** (0.1 g, 0.45 mmol) and pyridine (0.05 mL, 0.68 mmol) in dry DCM (5 mL) was added a solution of trifluoroacetic anhydride (70 μL, 0.50 mmol) in DCM (5 mL). The reaction mixture was stirred at r.t. for 4 h and then water (20 mL) was added. The organic layer was separated, dried and concentrated to dryness. The residue was subjected to a short column (silica gel; DCM)

to give compound **158** (0.13g, 92%) as a white solid; mp 168-170 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 2H, CH_2), 6.60 (d, *J*= 3.0 Hz, 1H, H-3), 7.03 (d, *J*= 3.0 Hz, 1H, H-2), 7.12-7.27 (m, 4H, Ar), 7.29 (t, *J*= 7.5 Hz, 1H, H-5′), 7.39 (t, *J*= 7.8 Hz, 1H, H-4′), 7.60 (d, *J*= 8.1 Hz, 1H, H-3′), 7.67 (dd, *J*= 6.6, 2.1 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 47.6 (CH_2), 103.0 (C-3), 109.4 (C-7), 115.5 (d, *J*= 285 Hz, ^{13}C-^{19}F, CF_3), 120.1 (C-5), 121.2 (C-4), 122.2 (C-6), 125.2 (C-3′), 127.3 (C-2), 127.9 (C-5′), 128.8 (C-3a), 129.0 (C-4′), 129.3 (C-6′), 130.7 (C-1′), 132.4 (C-2′), 136.1 (C-7a), 155.5 (d, *J*= 37.5 Hz, ^{13}C-^{19}F, CO-F); CI-MS *m/z* 319 ([M+H]$^{+}$, 100%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{17}H_{13}N_2OF_3$: 318.0980, found: 318.0990.

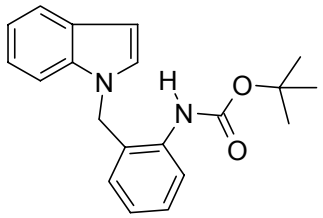
Synthesis of 1-[(2-*N*-ethylcarbamoylphenyl)methyl]-1*H*-indole (159)



To a stirred suspension of NaH (*ca* 50% dispersion in mineral oil, 23 mg, 0.49 mmol) in dry THF (5 mL) was added a solution of **149a** (0.10 g, 0.45 mmol) in dry THF (10 mL) under a N_2 atmosphere which was stirred at r.t. for 30 min. Ethyl chloroformate (65 μL, 0.68 mmol) in THF (10 mL) was then added and the reaction mixture stirred at r.t. overnight. The solvent was then removed under reduced pressure. DCM (15 mL) was added to the residue and the mixture was washed with water (3 x 15 mL). The organic extract was dried and concentrated to give a pink solid. The solid was passed through a quick column of silica gel eluting with 1:1 hexane/DCM to give the title compound **159** (130 mg, 98%) as white needles; mp 129-131 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J*= 7.2 Hz, 3H, $CH_2C\mathit{H}_3$), 4.20 (q, *J*= 7.2 Hz, 2H, $C\mathit{H}_2CH_3$), 5.29 (s, 2H, CH_2), 6.36 (br s, 1H, NH), 6.58 (dd, *J*= 3.0, 0.9 Hz, 1H, H-3), 6.92 (d, *J*= 7.8 Hz, 1H, H-3′), 7.05 (d, *J*= 3.0 Hz, 1H, H-2), 7.08 (ddd, *J*= 7.5, 7.5, 1.2 Hz, 1H, H-4′), 7.15 (dd, *J*= 7.5, 1.2, Hz, 1H, Ar), 7.20 (ddd, *J*= 7.5, 7.5, 1,2 Hz, 1H, Ar), 7.26-7.34 (m, 2H, Ar), 7.58 (d, *J*= 7.8 Hz, 1H, H-7), 7.67 (dt, *J*= 7.5, 1.2, 0.6 Hz,

1H, H-4); ^{13}C-NMR ($CDCl_3$) δ 15.0 (CH_2CH_3), 47.4 (CH_2), 61.9 (CH_2CH_3), 102.6 (C-3), 109.8 (C-7), 120.0 (C-5), 121.3 (C-4), 122.2 (C-6), 124.4, 125.9 (C-4′), 128.0 (C-2), 128.8 (C-3′), 128.9, 129.0, 135.4 (all ArC), 136.5 (C-7a), 154.5 (CO); CI-MS *m/z* 295 ($[M+H]^+$, 97%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{18}H_{18}N_2O_2$: 295.1447, found: 295.1446.

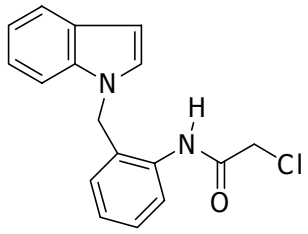
Synthesis of 1-[(2-*N*-*tert*-butoxycarbonylaminophenyl)methyl]-1*H*-indole (160)



To a stirred solution of NaH (*ca* 50% dispersion in mineral oil, 23 mg, 0.49 mmol) in dry THF (5 mL) was added amine **149a** (0.1 g, 0.45 mmol) in THF (10 mL) and the solution was stirred at r.t. for 30 min. $(BOC)_2O$ (0.15 g, 0.68 mmol) in THF (10 mL) was slowly added to the solution. The reaction mixture was further stirred at r.t. overnight. The solvent was evaporated to dryness. Diethyl ether (10 mL) was added and washed with water (3 x 10 mL). The organic layer was dried and evaporated to give a crude brown solid. The crude solid was subjected to flash column chromatography (silica gel, 1:1 hexane/DCM) to give the Boc compound **160** (0.13 g, 91%) as orange crystals; mp 139-141 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 9H, CH_3), 5.29 (s, 2H, CH_2), 6.20 (br s, 1H, NH), 6.56 (d, *J*= 3.3 Hz, 1H, H-3), 6.92 (d, *J*= 7.5 Hz, 1H, H-3′), 7.05-7.09 (m with prominent d, *J*= 3.3 Hz, 2H, H-2 and Ar), 7.12 (t, *J*= 7.5 Hz, 1H, H-5), 7.19 (t, *J*= 8.1 Hz, 1H, H-6), 7.25-7.32 (m, 2H, H-7 and Ar), 7.56 (d, *J*= 8.4 Hz, 1H, H-6′), 7.65 (d, *J*= 7.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 28.6 (CH_3), 47.4 (CH_2), 81.0 ($C(CH_3)_3$), 102.5 (C-3), 109.7 (C-7), 120.0 (C-5), 121.3 (C-4), 122.1 (C-6), 124.2 (ArC), 125.5 (C-4′), 128.0 (C-2), 128.7, 128.8 (all ArC-H), 128.9 (C-3a), 129.8 (C-1′), 135.7 (C-2′), 136.5 (C-7a), 153.5 (CO); CI-MS *m/z* 323 ($[M+H]^+$, 26%); HREI-MS *m/z* calcd for $[M]^+$ $C_{20}H_{22}N_2O_2$: 322.1680, found: 322.1697.

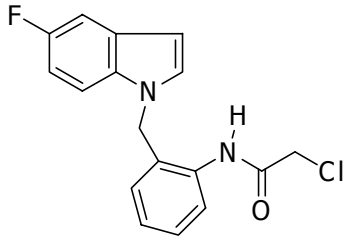
7.2.6 Preparation of chloroacetamides

Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}chloroacetamide (161)



A stirred suspension of amine **149a** (0.50 g, 2.2 mmol) and anhydrous K_2CO_3 (0.52 g, 3.74 mmol) in dry DCM (15 mL) was cooled to 0-5 ^oC and chloroacetyl chloride (0.26 mL, 3.30 mmol) in DCM (10 mL) was added. Stirring was continued with cooling for a further 30 min and the reaction then allowed to warm to r.t. with stirring overnight. Distilled water (15 mL) was added to the reaction and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a brown solid. The solid was subjected to flash column chromatography (silica gel, 1:1 DCM/hexane) to give the title compound **161** (0.55 g, 84%) as colourless, fluffy crystals; mp 123-124 ^oC (lit.[30] 120-122 ^oC); ^1H NMR ($CDCl_3$) δ 4.03 (s, 2H, CH_2Cl), 5.30 (s, 2H, CH_2), 6.57 (d, *J*= 3.3 Hz, 1H, H-3), 7.01 (d, *J*= 3.0 Hz, 1H, H-2), 7.07 (d, *J*= 7.5 Hz, 1H, Ar), 7.12-7.31 (m, 4H, Ar), 7.37 (t, *J*= 7.0 Hz, 1H, H-6), 7.65 (t, *J*= 7.2 Hz, 2H, H-4 and Ar), 8.00 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.7 (CH_2Cl), 47.3 (CH_2), 102.6 (C-3), 109.6 (C-7), 119.9 (ArC-H), 121.2 (C-1′), 122.0 (C-3′), 125.1 (C-2), 127.0 (C-3a), 127.4, 128.8, 128.9, 129.2, 130.4 (all ArC-H), 134.1 (C-7a), 136.4 (C-2′), 164.6 (CO); CI-MS *m/z* 299 ([M+H; $^{35}Cl]^+$, 100%).

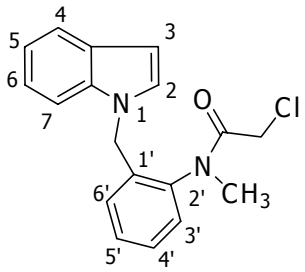
Synthesis of *N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]phenyl}chloroacetamide (162)



A stirred suspension of amine **149c** (0.15 g, 0.63 mmol) and anhydrous K_2CO_3 (95 mg, 0.69 mmol) in dry DCM (15 mL) was cooled to 0-5 ^oC and chloroacetyl chloride (75 μL, 0.94 mmol) in DCM (5 mL) was added. Stirring was continued with cooling for a further 30 min and the reaction then allowed to warm

to r.t. with stirring overnight. Distilled water (15 mL) was added to the reaction and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a brown solid. The solid was subjected to flash column chromatography (silica gel, 1:1 DCM/hexane) to give the title compound **162** (0.17 g, 86%) as colourless solid; mp 145-146 ^{o}C (lit.[30] 142-143 ^{o}C); ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 2H, CH_2Cl), 5.28 (s, 2H, CH_2), 6.51 (d, *J*= 3.0 Hz, 1H, H-3), 9.93 (d, *J*= 9.3, 2.4 Hz, 1H, H-6), 7.01-7.04 (m, 2H, Ar), 7.15- 7.25 (m, 2H, H-4 and Ar), 7.29 (dd, *J*= 9.6, 2.4 Hz, 1H, H-7), 7.37 (t, *J*= 7.8, 1.2 Hz, 1H, Ar), 7.61 (d, *J*= 7.8 Hz, 1H, H-3´), 8.00 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 43.1 (CH_2Cl), 48.0 (CH_2), 102.7 (d, *J*= 4.9 Hz, ^{13}C-^{19}F, C3-F), 106.1 (d, *J*= 23.3 Hz, ^{13}C-^{19}F, C6-F), 110.4 (C-7), 110.7 (d, *J*= 15.2 Hz, ^{13}C-^{19}F, C4-F), 125.4 (ArC-H), 126.0 (d, *J*= 14.4 Hz, ^{13}C-^{19}F, C3a-F), 127.4, 129.2, 129.3 (all ArC-H), 130.5 (C-1´), 133.2 (C-7a), 134.2 (C-2´), 158.1 (d, *J*= 234 Hz, ^{13}C-^{19}F, C5-F), 164.7 (CO); CI-MS *m/z* 317 ([M+H; ^{35}Cl]$^{+}$, 100%).

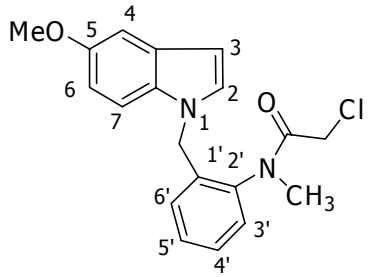
Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-methylchloroacetamide (163)



A mixture of **150a** (83 mg, 0.35 mmol) and anhydrous K_2CO_3 (0.18 g, 1.30 mmol) in dry DCM (5 mL) was cooled to 0-5 ^{o}C and chloroacetyl chloride (70 μL, 0.88 mmol) in DCM (3 mL) was added. Stirring was continued with cooling for a further 30 min and the reaction then allowed to warm to r.t. with stirring overnight. Distilled water (15 mL) was added to the reaction and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a yellow solid. The crude soild was subjected to flash column chromatography (silica gel, DCM) to give **163** (63 mg, 57%) as a colourless solid; mp 89-92 ^{o}C; IR (KBr) ν_{max}: 2852 (N-CH_3), 1658 (C=O), 796 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.24 (s, 3H, CH_3), 3.56 (d, *J*= 12.6 Hz, 1H, C*H*HCl), 3.66 (d, *J*= 12.6 Hz, 1H,

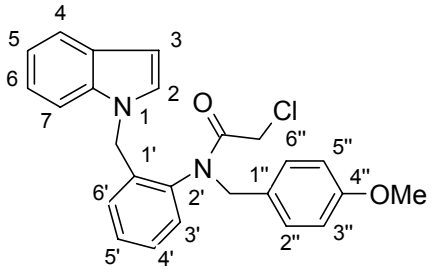
CH*H*Cl), 5.29 (d, *J*= 5.7 Hz, 2H, CH_2), 6.59 (d, *J*= 3.3 Hz, 1H, H-3), 6.99 (d, *J*= 7.5 Hz, 1H, Ar), 7.06 (d, *J*= 3.0 Hz, 1H, H-2), 7.11-7.39 (m, 5H, Ar), 7.36 (m, 1H, H-6), 7.67 (d, *J*= 7.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 37.5 (CH_3), 41.3 (CH_2Cl), 46.7 (CH_2), 102.7 (C-3), 109.6 (C-7), 119.9, 121.2 (C-1′), 122.0 (C-3′), 125.1 (C-2), 127.0 (C-3a), 127.4, 128.8, 128.9, 129.2, 130.4 (all ArC-H), 134.1 (C-7a), 136.4 (C-2′), 164.6 (CO); CI-MS *m/z* 313 $[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $C_{18}H_{18}N_2O^{35}Cl$: 313.1108, found: 313.1111.

Synthesis of *N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}-*N*-methylchloro acetamide (164)



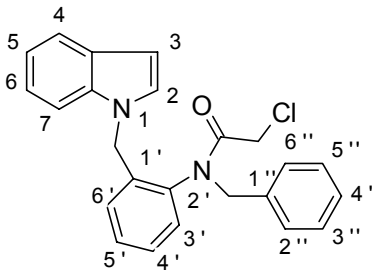
Following the procedure for **163**, treatment of **150b** (0.29 g, 1.09 mmol) with anhydrous K_2CO_3 (0.56 g, 4.03 mmol) and chloroacetyl chloride (0.22 mL, 2.73 mmol) gave **164** (0.22 g, 58%), after purification by column chromatography (silica gel, DCM), as a yellow solid; mp 71-73 ^oC; ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 3H, CH_3), 3.52 (d, *J*= 12.6 Hz, 1H, C*H*HCl), 3.62 (d, *J*= 12.6 Hz, 1H, CH*H*Cl), 3.83 (s, 3H, OCH_3), 5.23 (d, *J*= 5.1 Hz, 2H, CH_2), 6.84 (d, *J*= 3.6 Hz, 1H, C-3), 6.83 (dd, *J*= 9.0, 2.4 Hz, 1H, Ar), 6.87 (d, *J*= 7.5 Hz, 1H, Ar), 7.02 (d, *J*= 3.0 Hz, 1H, H-2), 7.05-7.10 (m with prominent d, *J*= 2.4 Hz, 2H, Ar), 7.20 (dd, *J*= 7.5, 1.2 Hz, 1H, Ar), 7.28- 7.39 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 37.5 (CH_3), 41.2 (CH_2Cl), 47.1 (CH_2), 56.1 (OCH_3), 102.3 (C-3), 103.0, 110.4, 112.6, 128.9, 129.0 (all ArC-H), 129.3 (C-3a), 129.7, 129.9, 131.6 (C-1′), 135.2 (C-7a), 140.6 (C-2′), 154.4 (*C*OCH_3), 166.8 (CO); CI-MS *m/z* 343 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{19}H_{20}N_2O_2{}^{35}Cl$: 343.1213, found: 343.1208.

Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-(4-methoxybenzyl)chloro acetamide (165)



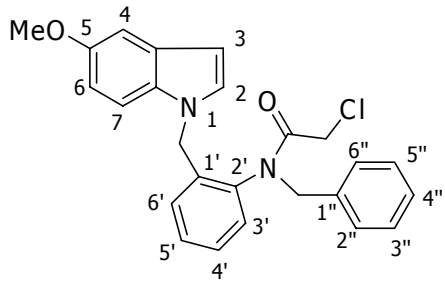
To a stirred suspension of NaH (27 mg *ca* 50% dispersion in mineral oil, 0.57 mmol) in dry THF (5 mL) was added a solution of **152** (0.18 g, 0.52 mmol) in dry THF (20 mL) under a N_2 atmosphere with stirring at r.t. for 30 min. Chloroacetyl chloride (0.11 mL, 1.42 mmol) in THF (5 mL) was then added and the reaction mixture stirred overnight. The solvent was then removed under reduced pressure. DCM (15 mL) was added to the residue and the mixture was washed with water (3 x 15 mL). The organic layer was dried and concentrated to give a yellow residue. The residue was subjected to a flash column of silica gel by eluting with DCM to give **165** (0.20 g, 93%) as a yellow solid; mp 82-84 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.51 (d, *J*= 12.6 Hz, 1H, C*H*HCl), 3.62 (d, *J*= 12.6 Hz, 1H, CH*H*Cl), 3.75 (s, 3H, OCH_3), 4.55 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.78 (d, *J*= 16.8 Hz, 1H, C*H*H), 4.95 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 5.08 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.51 (d, *J*= 3.3 Hz, 1H, H-3), 6.77-6.80 (m with prominent d, *J*= 8.7 Hz, 3H, H-3′, H-3′′, and H-5′′), 6.84-6.88 (m with prominent d, *J*= 3.0 Hz, 2H, H-2 and H-6′), 7.00 (d, *J*= 8.1 Hz, 1H, Ar), 7.07 (t, *J*= 7.2 Hz, 1H, H-5), 7.09-7.12 (m with prominent d, *J*= 8.7 Hz, 3H, H-6, H-2′′, and H-6′′), 7.17-7.24 (m, 2H, Ar), 7.59 (d, *J*= 7.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 41.8 (CH_2Cl), 46.6 (CH_2), 53.8 (CON*C*H_2), 55.6 (CH_3), 102.7 (C-3), 109.6, 114.3, 120.8, 121.4, 122.3, 128.2, 128.3 (all ArC-H), 128.8 (C-3a), 129.3, 129.4, 129.9, 130.1, 131.3 (all ArC-H), 135.9 (C-1′), 136.4 (C-7a), 138.4 (C-2′), 159.7 (*C*OCH_3), 166.8 (CO); CI-MS *m/z* 419 ($[M+H]^+$; 100%), 421 ($[M+H]^+$; $^{37}Cl]^+$, 35%); HRCI-MS *m/z* calcd for $C_{25}H_{24}N_2O_2{}^{37}Cl$: 421.1497, found: 421.1498.

Synthesis of *N*-benzyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl}chloroacetamide (166)



Following the procedure for **165**, NaH (*ca* 50% dispersion in mineral oil, 70 mg, 1.76 mmol) was reacted with **153** (0.50 g, 1.60 mmol) and chloroacetyl chloride (0.32 mL, 4.00 mmol) to give **166** (0.50 g, 81%), after purification by column chromatography (silica gel, DCM), as a yellow solid; mp 148-149 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.56 (d, *J*= 12.9 Hz, 1H, C*H*HCl, 3.66 (d, *J*= 13.2 Hz, 1H, CH*H*Cl), 4.65 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.80 (d, *J*= 16.8 Hz, 1H, C*H*H), 5.04 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.12 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.54 (d, *J*= 3.0 Hz, 1H, H-3), 6.78 (m, 1H, Ar), 6.85 (d, *J*= 3.0 Hz, 1H, H-2), 6.93 (m, 1H, Ar), 7.04 (d, *J*= 7.8 Hz, 1H, H-7), 7.13 (td, *J*= 7.2, 1.5 Hz, 1H, H-5), 7.22 (td, *J*= 6.9, 0.9 Hz, 1H, H-6), 7.22-7.28 (m, 4H, Ar), 7.30-7.36 (m, 3H, Ar), 7.64 (dd, *J*= 7.5, 0.9 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ 41.3 (CH_2Cl), 46.3 (CH_2), 53.3 (CON*C*H_2), 102.5 (C-3), 109.3 (C-7), 119.5 (C-5), 121.2 (C-4), 122.1 (C-6), 127.9 (C-2), 128.3, 128.5 (C-3a), 128.8, 129.0, 129.2, 129.7, 129.8, 129.9 (all ArC-H), 135.7 (C-1′), 136.0 (C-7a), 136.2 (C-1′′), 138.3 (C-2′), 166.5 (CO); CI-MS *m/z* 388 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{21}N_2O^{35}Cl$: 388.1342, found: 388.1334.

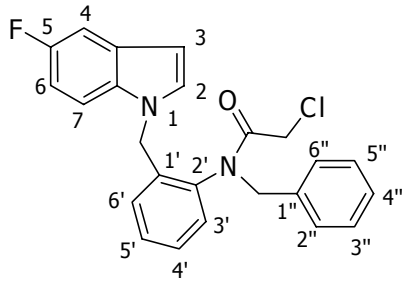
Synthesis of *N*-benzyl-*N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}chloro acetamide (167)



Following the procedure for **165**, NaH (*ca* 50% dispersion in mineral oil, 23 mg, 0.64 mmol) was reacted with **154** (0.20 g, 0.58 mmol) and chloroacetyl chloride (0.12 mL, 1.45 mmol) to give **167** (0.14 g, 58%), after purification by column chromatography (silica gel, DCM), as a yellow solid; mp 166-169 ^{o}C; ^{1}H NMR ($CDCl_3$)

δ 3.54 (d, *J*= 12.9 Hz, 1H, C*H*HCl), 3.64 (d, *J*= 12.9 Hz, 1H, CH*H*Cl), 3.83 (s, 3H, OCH_3), 4.62 (d, *J*= 13.5 Hz, 1H, CONC*H*H), 4.78 (d, *J*= 16.5 Hz, 1H, C*H*H), 5.04 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.08 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.46 (d, *J*= 2.4 Hz, 1H, H-3), 6.79- 6.84 (m, 3H, Ar), 6.90-6.93 (m, 2H, Ar), 7.08 (d, *J*= 2.4 Hz, 1H, H-4), 7.21-7.33 (m, 7H, Ar); ^{13}C NMR ($CDCl_3$) δ 41.6 (CH_2Cl), 46.8 (CH_2), 53.5 (CON*C*H_2), 56.0 (CH_3), 102.2 (C-3), 110.3, 112.6, 128.5, 128.7, 128.9, 129.2 (C-3a), 129.3, 129.5, 129.9, 130.0, 130.1 (all ArC-H), 131.7 (C-1′), 136.0 (C-7a), 136.3 (C-1′′), 138.6 (C-2′), 154.5 (*C*OCH_3), 166.7 (CO); CI-MS *m/z* 419 [(M+H;^{35}Cl]$^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{24}N_2O_2{}^{35}Cl$: 419.1526, found: 419.1506.

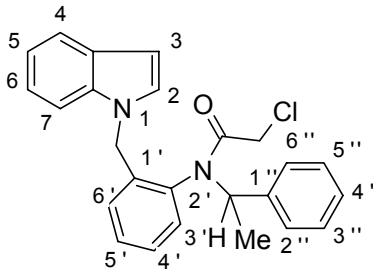
Synthesis of *N*-benzyl-*N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]phenyl}chloro acetamide (168)



Following the procedure for **165**, NaH (*ca* 50% dispersion in mineral oil, 18 mg, 0.46 mmol) was reacted with **153** (0.14 g, 0.42 mmol) and chloroacetyl chloride (84 μL, 1.05 mmol) to give **168** (0.13 g, 76%), after purification by column chromatography (silica gel, DCM), as a yellow solid; mp 135-136 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.55 (d, *J*= 12.6 Hz, 1H, C*H*HCl), 3.67 (d, *J*= 12.9 Hz, 1H, CH*H*Cl), 4.64 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.79 (d, *J*= 16.8 Hz, 1H, C*H*H), 5.02 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.11 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.50 (d, *J*= 3.3 Hz, 1H, H-3), 6.79 (ddd, *J*= 9.3, 8.1, 2.7 Hz, 1H, Ar), 6.90 (d, *J*= 3.3 Hz, 1H, H-2), 6.91-6.97 (m, 3H, Ar), 7.22-7.34 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$) δ 41.5 (CH_2Cl), 46.8 (CH_2), 53.6 (CON*C*H_2), 102.7 (d, *J*= 4.6 Hz, ^{13}C-^{19}F, C-3), 106.2 (d, *J*= 23.0 Hz, ^{13}C-^{19}F, C-6), 110.2 (d, *J*= 9.8 Hz, ^{13}C-^{19}F, C-7), 110.7 (d, *J*= 26 Hz, ^{13}C-^{19}F, C-4), 128.6, 129.0, 129.2, 129.3, 129.5 (C-3a), 129.7, 129.8, 130.0, 130.2, 133.1 (C-1′), 135.7 (C-

7a), 136.2 (C-1′′), 138.6 (C-2′), 158.2 (d, *J*= 223.6 Hz, ^{13}C-^{19}F, C5-F), 166.9 (CO); CI-MS *m/z* 407 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{24}H_{21}N_2O^{35}ClF$: 407.1326, found: 407.1319.

Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-(1-phenylethyl)chloro acetamide (169)



A mixture of **156** (87 mg, 0.27 mmol), triethylamine (56 µL, 0.41 mmol) and DMAP (3.3 mg, 0.03 mmol) in dry DCM (10 mL) was stirred at 0 ^oC. To this solution was then added a solution of chloroacetyl chloride (60 µL, 0.54 mmol) in dry DCM (2 mL) and the mixture was stirred at r.t. for 1 h. The reaction mixture was washed with brine (15 mL) and the DCM layer was dried and concentrated. The residue was subjected to flash column chromatography (silica gel, 1:1 hexane/DCM) to give **169** (36 mg, 33%) as a white solid; mp 90-92 ^oC; ^1H NMR ($CDCl_3$, rotamer ratio of *ca* 2:1*, * = minor rotamer) δ 1.58* (d, *J*= 7.2 Hz, 1H, CH_3) 1.64 (d, *J*= 7.2 Hz, 2H, CH_3), 3.53 (d, *J*= 13.2 Hz, 1H, C*H*HCl), 3.63 (d, *J*= 13.2 Hz, 1H, CH*H*Cl), 3.73 (d, *J*= 17.4 Hz, 0.7H, C*H*H), 4.63 (d, *J*= 17.4 Hz, 0.7H, CH*H*), 5.31* (d, *J*= 17.1 Hz, 0.3H, C*H*H), 5.37* (d, *J*= 17.1 Hz, 0.3H, CH*H*), 6.22* (q, *J*= 7.2 Hz, 0.3Hz, CH), 6.30 (q, *J*= 7.2 Hz, 0.7H, CH), 6.40 (d, *J*= 7.8 Hz, 0.7H, H-3′), 6.50 (d, *J*= 3.3 Hz, 0.7H, H-3), 6.51 (d, *J*= 3.0 Hz, 0.7H, H-2), 6.60* (d, *J*= 3.3 Hz, 0.3H, H-3), 6.78 (d, *J*= 7.8 Hz, 1H, Ar), 7.02-7.04* (m, 0.6H, H-2 and Ar), 7.06-7.16 (m, 3.4H, H-2′′, H-6′′ and Ar), 7.22 (td, *J*= 7.5, 1.5 Hz, 1H, H-4′ and H-4′*), 7.27-7.36 (m, 5H, H-3′′, H-5′′ and Ar), 7.39-7.43 (m, 1H, H-7 and H-7*), 7.58 (dd, *J*= 8.1, 2.1 Hz, 0.7H, H-4), 7.67* (d, *J*= 7.8 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_3), 42.3 (CH_2Cl), 46.0 (CH_2), 55.7 (CH), 102.5 (C-3), 109.4, 119.9 (C-5), 121.2 (C-4), 122.1, 128.0 (C-2), 128.4 (C-3′), 128.5 (C-3a), 128.6, 128.9, 129.5, 130.2, 131.4, 134.9 (C-1′), 136.5 (C-

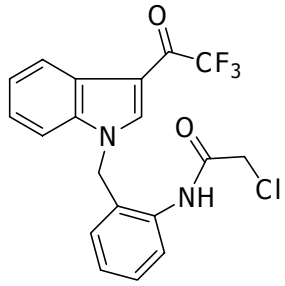
7a), 138.3 (C-1′′), 139.1 (C-N), 166.3 (CO); CI-MS *m/z* 403 ($[M+H]^+$, 100%), 369 ($[MH-Cl]^+$, 52%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{24}N_2O^{35}Cl$: 403.1577, found: 403.1559.

Attempted synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-trifluoroacetyl chloroacetamide (170)

Method A: A mixture of **158** (0.10 g, 0.31 mmol) and anhydrous K_2CO_3 (48 mg, 0.35 mmol) in dry DCM (20 mL) was cooled to 0-5 ^oC and chloroacetyl chloride (38 μL, 0.47 mmol) in DCM (3 mL) was added. Stirring was continued with cooling for a further 30 min and the reaction mixture was then allowed to warm to r.t. with stirring overnight. Distilled water (20 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a crude yellow solid (0.12 g). ^1H NMR of the crude solid showed that mostly starting material was recovered.

Method B: To a stirred solution of NaH (*ca* 50% dispersion in mineral oil, 18 mg, 0.38 mmol) in dry DMF (5 mL) was added amine **158** (0.10 g, 0.31 mmol) in DMF (15 mL) and the solution was stirred at r.t. for 30 min. $(CF_3CO)_2O$ (0.12 mL, 0.85 mmol) in DMF (5 mL) was slowly added to the solution. The reaction mixture was then stirred at r.t. overnight. The solvent was then evaporated to dryness. Diethyl ether (10 mL) was added and washed with water (3 x 10 mL). The organic layer was dried and evaporated to give a crude orange solid (0.28 g). ^1H NMR of the crude solid showed only starting material was recovered.

Synthesis of *N*-{2-[1-(3-trifluoroacetyl-1*H*-indolyl)methyl]phenyl}chloroacetamide (171)



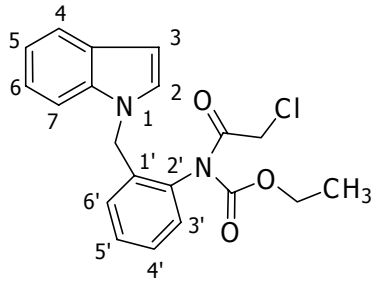
To a stirred solution of the chloroacetamide **161** (0.13 g, 0.45 mmol) and pyridine (0.05 mL, 0.68 mmol) in dry DCM (5 mL) was added a solution of trifluoroacetic anhydride (70 μL, 0.50 mmol) in DCM (5 mL). The reaction mixture was stirred at r.t. for 4 h and then water (20 mL) was added. The organic layer was separated, dried and concentrated to dryness. The residue was subjected to PTLC (silica gel, DCM) to give starting material **161** (70 mg, 51%, higher R_f) and compound **171** as a white solid (lower R_f) (12 mg, 7%); mp 203-204 ^oC; ^1H NMR ($CDCl_3$) δ 4.16 (s, 2H, CH_2Cl), 5.42 (s, 2H, CH_2), 6.97 (d, *J*= 7.5 Hz, 1H, H-3′), 7.25-7.43 (m, 6H, Ar), 7.92 (d, *J*= 1.8 Hz, 1H, H-2), 8.13 (br s, 1H, NH), 8.41 (d, *J*= 7.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 43.0 (CH_2Cl), 48.7 (CH_2), 110.4 (C-3), 110.9 (C-7), 117.2 (d, *J*= 285 Hz, ^{13}C-^{19}F, CF_3), 123.0 (C-4), 124.4 (C-5′), 125.1 (C-6), 126.4 (C-5), 127.3 (C-3a), 128.3 (C-4′), 128.5 (C-3′), 129.7 (C-6′), 130.6 (C-1′), 133.5 (C-2′), 137.1 (C-7a), 137.8 (C-2), 155.2 (d, *J*= 37.5 Hz, ^{13}C-^{19}F, CO-F), 165.1 (CO); CI-MS *m/z* 395 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd. for $[M]^+$ $C_{19}H_{14}N_2O_2{}^{35}ClF_3$: 394.0696, found: 394.0689.

Attempted synthesis of *N*-ethoxycarbonyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl} chloroacetamide (172)

A mixture of **159** (0.10 g, 0.34 mmol) and anhydrous K_2CO_3 (80 mg, 0.58 mmol) in dry DCM (20 mL) was cooled to 0-5 ^oC and chloroacetyl chloride (41 μL, 0.51 mmol) in DCM (3 mL) was then added. Stirring was continued with cooling for a further 30 min and the reaction was then allowed to warm to r.t. with stirring overnight. Distilled water (20 mL) was added to the reaction mixture and the aqueous layer was extracted

with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a crude yellow solid (0.12 g). ^{1}H NMR of the crude solid showed that only starting material was recovered.

Synthesis of *N*-ethoxycarbonyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl}chloro acetamide (172)



To a stirred solution of NaH (*ca* 50% dispersion in mineral oil, 18 mg, 0.38 mmol) in dry DMF (5 mL) was added a solution of chloroacetamide **161** (0.10 g, 0.35 mmol) in DMF (15 mL) and the solution mixture was stirred at r.t. for 30 min. Ethyl chloroformate (81 μL, 0.85 mmol) in DMF (5 mL) was slowly added to the solution. The reaction mixture was then stirred at r.t. overnight. The solvent was evaporated to dryness. Diethyl ether (10 mL) was added and washed with water (3 x 10 mL). The organic layer was dried and evaporated to give a crude orange solid (0.13 g). The crude solid was subjected to flash column chromatography (silica gel, 70:30 DCM/hexane) to give compound **172** (40 mg, 32%); mp 45-47 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 1.09 (t, *J*= 7.2 Hz, 3H, CH_2CH_3), 3.92 (ddd, *J*= 7.2, 7.2, 6.9 Hz, 1H, C*H*HCH$_3$), 4.08 (ddd, *J*= 7.2, 7.2, 6.9 Hz, 1H, CH*H*CH$_3$), 4.77 (s, 2H, CH_2Cl), 5.12 (d, *J*= 16.2 Hz, 1H, C*H*H), 5.21 (d, *J*= 16.2 Hz, 1H, CH*H*), 6.54 (d, *J*= 3.0 Hz, 1H, H-3), 6.98 (dd, *J*= 7.5, 1.8 Hz, 1H, H-3′), 7.03 (d, *J*= 3.3 Hz, 1H, H-2), 7.07 (dd, *J*= 7.5, 1.8 Hz, 1H, H-6′), 7.08-7.15 (m, 3H, H-5, H-6, and H-7), 7.30 (td, *J*= 7.2, 1.8 Hz, 1H, H-4′), 7.36 (td, *J*= 7.5, 1.8 Hz, 1H, H-5′), 7.64 (dd, *J*= 6.9, 1.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 46.3 (CH_2), 47.1 (CH_2Cl), 64.2 (*C*H_2CH_3), 102.3 (C-3), 109.7 (C-7), 119.9 (C-5), 121.3 (C-4), 122.0 (C-6), 128.5 (C-2), 128.8 (C-3′), 128.9 (C-3a), 129.06 (C-6′), 129.1 (C-5′), 129.6 (C-4′), 135.1 (C-1′), 135.6 (C-7a),

136.4 (C-2′), 153.3 (COO), 168.8 (CO); CI-MS *m/z* 371 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{20}H_{19}N_2O_3{}^{35}Cl$: 370.1084, found: 370.1094.

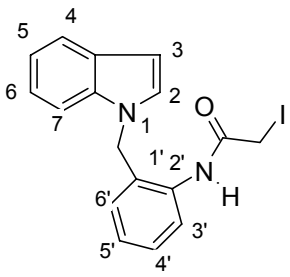
Attempted synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-*tert*-butoxycarbonyl chloroacetamide (173)

Method A: To a stirred solution of NaH (*ca* 50% dispersion in mineral oil, 16 mg, 0.34 mmol) in dry THF (5 mL) was added the compound **160** (0.10 g, 0.31 mmol) in THF (10 mL) and the solution was stirred at r.t. for 30 min. Chloroacetyl chloride (60 μL, 0.76 mmol) in THF (5 mL) was then slowly added to the solution. The reaction mixture was then stirred at r.t. overnight. The solvent was evaporated to dryness and water (20 mL) was added and the mixture extracted with DCM (3 x 15 mL). The organic layer was dried and evaporated to give a crude pale orange solid (0.13 g). The crude solid was subjected to flash column chromatography (silica gel, 70:30 DCM/hexane), however, only starting material **160** (60 mg) was recovered.

Method B: A mixture of **160** (80 mg, 0.25 mmol), triethylamine (56 μL, 0.41 mmol) and DMAP (3.3 mg, 0.03 mmol) in dry DCM (10 mL) was stirred at 0 ^oC. To this solution was added a solution of chloroacetyl chloride (60 μL, 0.54 mmol) in dry DCM (2 mL) and the mixture was stirred at r.t. for 1 h. The reaction mixture was washed with brine (15 mL) and the organic layer was dried and concentrated. The residue was subjected to flash column chromatography (silica gel, DCM) to give, in the first fraction, the chloroacetamide **161** (23 mg, 31%) and, in the second fraction, the starting material **160** (42 mg, 52%).

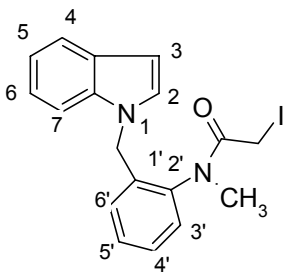
7.2.7 Preparation of iodoacetamides

Synthesis of N-{2-[1-(1*H*-indolyl)methyl]phenyl}iodoacetamide (174)



A solution of **161** (73 mg, 0.24 mmol) in acetronitrile (5 mL) containing NaI (0.37 g, 2.48 mmol) was heated at reflux for 2 h. The solution was then cooled and water (10 mL) was added. The solution was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried and concentrated. The residue was purified by flash column chromatography (silica gel, DCM) to give the title compound **174** as a colourless solid (83 mg, 0.21 mmol, 87%); mp 101-103 ^{o}C; IR (KBr) ν_{max}: 2853 (N-CH_3), 1659 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.53 (s, 2H, CH_2I), 5.27 (s, 2H, CH_2), 6.58 (d, *J*= 3.3 Hz, 1H, H-3), 7.03 (br d, *J*= 3.3 Hz, 2H, H-2 and Ar), 7.12-7.26 (m, 3H, Ar), 7.29-7.32 (m, 2H, Ar and NH), 7.53 (br.d, *J*= 7.5 Hz, 2H, H-6 and Ar), 7.67 (d, *J*=7.2 Hz, 1H, H-4); ^{13}C-NMR ($CDCl_3$) δ -3.1 (CH_2I), 47.5 (CH_2), 102.9 (C-3), 109.8 (C-7), 120.3, 121.5, 122.4, 125.3, 127.1, 127.9, 129.0, 129.2, 131.0, 134.8, 136.5 (C-N), 166.4 (CO); EI-MS *m/z* 390 ($[M]^+$, 52%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{15}N_2OI$: 390.0229, found: 390.0232.

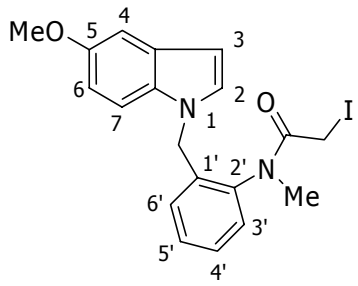
Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-methyliodoacetamide (175)



Following the procedure for **174**, treatment of **163** (0.10 g, 0.32 mmol) with NaI (0.50 g, 3.32 mmol) in refluxing acetonitrile (5 mL) gave **175** (after purification by column chromatography with DCM; 0.12 g, 93%) as a yellow solid; mp 53-54 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 3.21 (s, 3H, CH_3), 3.30 (d, *J*= 10.2 Hz, 1H, C*H*HI), 3.45 (d, *J*= 9.6 Hz, 1H, CH*H*I), 5.25 (d, *J*= 16.5 Hz, 1H, C*H*H), 5.37 (d, *J*= 16.5 Hz, 1H, CH*H*) 6.58 (d, *J*= 2.7 Hz, 1H, H-3), 6.96 (d, *J*= 8.4 Hz, 1H, Ar), 7.09 (d, *J*= 3.0 Hz, 1H, H-2). 7.11-7.39

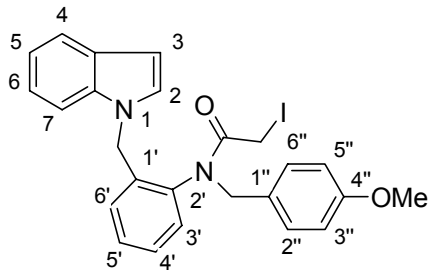
(m, 6H, Ar), 7.66 (d, *J*= 7.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ -2.9 (CH_2I), 37.7 (CH_3), 47.0 (CH_2), 102.7 (C-3), 109.7 (C-7), 120.1, 121.4, 122.3, 128.3, 128.5 (all ArC-H), 128.6 (C- 3a), 128.9, 129.6, 129.8 (all ArC-H), 134.9 (C-1′), 136.4 (C-7a), 141.3 (C-2′), 168.3 (CO); CI-MS *m/z* 405 ([M+H]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$ $C_{18}H_{17}N_2OI$: 404.0386, found: 404.0396.

Synthesis of *N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}-*N*-methyl iodoacetamide (176)



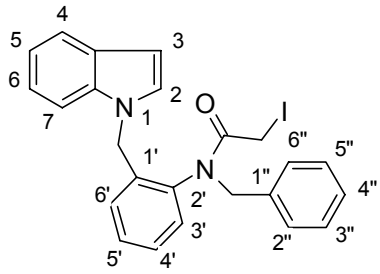
Following the procedure for **174**, treatment of **164** (0.21g, 0.63 mmol) with NaI (0.99 g, 6.61 mmol) in refluxing acetonitrile (10 mL) gave **176** (after purification by column chromatography with DCM; 0.17g, 70%) as a yellow solid; mp 75-77 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 31.8 (s, 3H, CH_3), 3.27 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.42 (d, *J*= 10.2 Hz, 1H, CH*H*I), 3.83 (s, 3H, OCH_3), 5.26 (d, *J*= 16.2 Hz, 1H, C*H*H), 5.37 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.48 (d, *J*= 3.3 Hz, 1H, H-3), 6.83 (dd, *J*= 8.7, 2.7 Hz, 1H, Ar), 6.93 (dd, *J*= 7.2, 2.1 Hz, 1H, Ar), 7.05 (d, *J*= 3.0 Hz, 1H, H-2), 7.08-7.11 (m, 2H, Ar), 7.23 (td, *J*= 8.4, 1.5 Hz, 1H, Ar), 7.35 (d, *J*= 8.7 Hz, 1H, Ar), 7.38 (d, *J*= 9.3 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ -2.7 (CH_2I), 37.7 (CH_3), 47.2 (CH_2), 56.1 (OCH_3), 102.3 (C-3), 103.0, 110.5, 112.6, 128.5, 128.9, 129.6, 129.8, 131.7 (C-1′), 135.0 (C-7a), 141.3 (C-2′), 154.4 (*C*OCH_3), 168.3 (CO); CI-MS *m/z* 435 ([M+H]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$ $C_{19}H_{19}N_2O_2I$: 434.0491, found: 434.0476.

Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-(4-methoxybenzyl)-iodoacetamide (177)



Following the procedure for **174**, treatment of **165** (0.20g, 0.48 mmol) with NaI (0.76 g, 5.04 mmol) in refluxing acetonitrile (10 mL) gave **177** (after purification by column chromatography with DCM; 0.17g, 70%) as a yellow solid; mp 64-65 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.20 (d, *J*= 9.6 Hz, 1H, C*H*HI), 3.35 (d, *J*= 9.9 Hz, 1H, CH*H*I), 3.72 (s, 3H, OCH_3), 4.51 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.77 (d, *J*= 16.8 Hz, 1H, C*H*H), 4.87 (d, *J*= 14.1 Hz, 1H, CONCH*H*), 5.10 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.47 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.70 (dd, *J*= 8.1, 2.4 Hz, 1H, H-3′), 6.76 (dd, *J*= 9.0, 2.4 Hz, 2H, H-3′′ and H-5′′), 6.82 (d, *J*= 3.0 Hz, 1H, H-2), 6.95 (dd, *J*= 9.0, 2.4 Hz, 1H, H-6′), 6.98 (d, *J*= 8.4 Hz, 1H, Ar), 7.04 (td, *J*= 6.9, 1.2 Hz, 1H, H-5), 7.05-7.12 (m with prominent d, *J*= 8.7 Hz, 3H, H-6, H-2′′ and H-6′′), 7.14-7.23 (m, 2H, Ar), 7.56 (dd, *J*= 7.5, 0.9 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ -2.0 (CH_2I), 46.8 (CH_2), 53.1 (CON*C*H_2), 55.6 (CH_3), 102.7 (C-3), 109.7, 114.3, 120.1, 121.4, 122.2, 128.2, 128.5, 128.7 (C-3a), 129.3, 129.8, 131.2, 135.6 (C-1′′), 136.5 (C-7a), 139.2 (C-2′), 159.7 (*C*OCH_3), 168.0 (CO); CI-MS *m/z* 511 ($[M+H]^+$, 13%); HREI-MS *m/z* calcd for $[M]^+$ $C_{25}H_{23}N_2O_2I$: 510.0804, found: 510.0810.

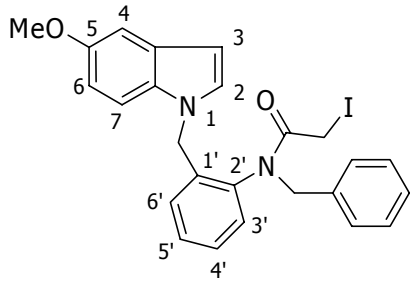
Synthesis of *N*-benzyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl]iodoacetamide (178)



Following the procedure for **174**, treatment of **166** (0.50 g, 1.29 mmol) with NaI (1.90 g, 12.9 mmol) in refluxing acetonitrile (20 mL) gave **178** (after purification by column chromatography with DCM; 0.52 g, 96%) as a yellow solid; mp 101-103 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.31 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.46 (d, *J*= 9.6 Hz, 1H, CH*H*I), 4.62 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.85

(d, *J*= 16.8 Hz, 1H, C*H*H), 5.04 (d, *J*= 14.1 Hz, 1H, CONCH*H*), 5.18 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.55 (d, *J*= 3.3 Hz, 1H, H-3), 6.79 (dd, *J*= 7.5, 2.7 Hz, 1H, Ar), 6.88 (d, *J*= 3.3 Hz, 1H, H-2), 7.03 (d, *J*= 6.9 Hz, 1H, Ar), 7.06 (d, *J*= 7.5 Hz, 1H, H-7), 7.11(td, *J*= 6.6, 0.9 Hz, 1H, H-5), 7.18 (td, *J*= 7.5, 1.2 Hz, 1H, H-6), 7.22-7.28 (m, 4H, Ar), 7.30-7.36 (m, 3H, Ar), (7.64 (dd, *J*= 7.8, 1.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ -2.2 (CH_2I), 46.8 (CH_2), 53.7 (CON*C*H_2), 102.7 (C-3), 109.6, 120.6, 121.4, 122.2, 128.1 (C-2), 128.4, 128.8 (C-3a), 128.9, 129.2, 129.3, 129.7, 129.8, 129.9, 135.6 (C-1′), 136.4 (C-7a), 136.5 (C-1′′), 139.3 (C-2′), 168.1 (CO); EI-MS *m/z* 480 ($[M]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{21}N_2OI$: 480.0690, found: 480.0689.

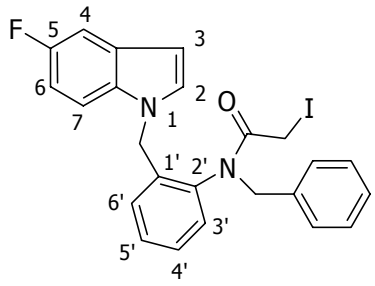
Synthesis of *N*-benzyl-*N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}iodo acetamide (179)



Following the procedure for **174**, treatment of **167** (62 mg, 0.15 mmol) with NaI (0.22 g, 1.50 mmol) in refluxing acetonitrile (5 mL) gave **179** (after purification by column chromatography with DCM; 55 mg, 73%) as a yellow solid; mp 59-61 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.28 (d, *J*= 9.6 Hz, 1H, C*H*HI), 3.43 (d, *J*= 9.9 Hz, 1H, CH*H*I), 3.84 (s, 3H, OCH_3), 4.60 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.81 (d, *J*= 16.8 Hz, 1H, C*H*H), 5.02 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.12 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.46 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.78-6.81 (m, 2H, Ar), 6.83-6.86 (m, 2H, H-2 and Ar), 6.93 (dd, *J*= 9.0, 0.6 Hz, 1H, H-3′), 7.05 (ddd, *J*= 9.0, 6.6, 2.4 Hz, 1H, Ar), 7.09 (d, *J*= 2.4 Hz, 1H, H-4), 7.27-7.29 (m, 4H, Ar), 7.33-7.36 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ -2.5 (CH_2I), 46.9 (CH_2), 53.5 (CON*C*H_2), 56.0 (OCH_3), 102.2 (C-3), 102.9, 110.4, 112.5, 128.4, 128.6 (C-3a), 128.7, 128.9, 129.2, 129.4, 129.7, 129.8, 129.9, 131.8 (C-1′), 135.7 (C-7a),

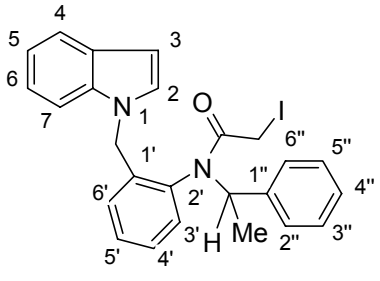
136.5 (C-1′′), 139.4 (C-2′), 154.5 (*C*OCH$_3$), 168.2 (CO); CI-MS *m/z* 511 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{25}H_{24}IN_2O_2$: 511.0883, found: 511.0868.

Synthesis of *N*-benzyl-*N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]phenyl}iodoacetamide (180)



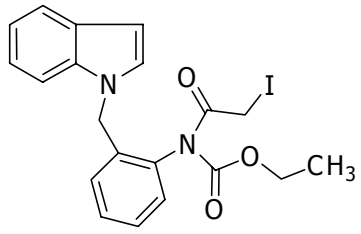
Following the procedure for **174**, treatment of **168** (74 mg, 0.18 mmol) with NaI (0.27 g, 1.80 mmol) in refluxing acetonitrile (5 mL) gave **180** (after purification by column chromatography with DCM; 77 mg, 89%) as a yellow solid; mp 53-54 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.28 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.42 (d, *J*= 9.0 Hz, 1H, CH*H*I), 4.64 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.82 (d, *J*= 16.8 Hz, 1H, C*H*H), 4.98 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.15 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.49 (d, *J*= 3.3 Hz, 1H, H-3), 6.77 (dd, *J*= 7.5, 2.7 Hz, 1H, Ar), 6.90-6.93 (m with prominent d, *J*= 3.0 Hz, 3H, H-2 and Ar), 7.05 (dd, *J*= 8.9, 2.7 Hz, 1H, Ar), 7.22-7.33 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$) δ -2.6 (CH_2I), 47.0 (CH_2), 53.6 (CONCH_2), 102.6 (d, *J*= 5.2 Hz, ^{13}C-^{19}F, C-3), 106.1 (d, *J*= 22.9 Hz, ^{13}C-^{19}F, C-6), 110.3 (d, *J*= 9.8 Hz, ^{13}C-^{19}F, C-7), 110.7 (d, *J*= 26.3 Hz, ^{13}C-^{19}F, C-4), 128.5, 129.0, 129.2, 129.6, 129.79, 129.83, 129.88, 129.9, 130.5 (C-3a), 133.1 (C-1′), 135.4 (C-7a), 136.5 (C-1′′), 139.4 (C-2′), 158.2 (d, *J*= 223.7 Hz, ^{13}C-^{19}F, C5-F), 168.2 (CO); CI-MS *m/z* 499 ([M+H]$^+$, 46%); HREI-MS *m/z* calcd for [M]$^+$ $C_{24}H_{20}N_2OFI$: 498.0604, found: 498.0600.

Synthesis of *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-(1-phenylethyl)iodoacetamide (181)



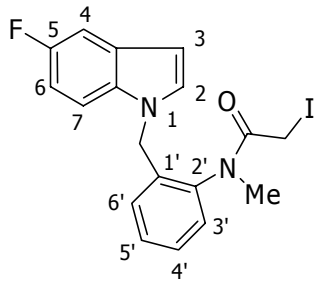
Following the procedure for **174**, treatment of **169** (36 mg, 0.09 mmol) with NaI (0.14 g, 0.95 mmol) in refluxing acetonitrile (3 mL) gave **181** (after purification by column chromatography with DCM, 37 mg, 82%) as a yellow solid; mp 60-61 ^{o}C; ^{1}H NMR ($CDCl_3$, isomer ratio of *ca* 2:1*) δ 1.55* (d, *J*= 7.2 Hz, 1H, CH_3), 1.62 (d, *J*= 6.9 Hz, 2H, CH_3), 3.24 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.44 (d, *J*= 9.6 Hz, 1H, CH*H*I), 3.80 (d, *J*= 17.1 Hz, 0.7H, C*H*H), 4.69 (d, *J*= 17.1 Hz, 0.7H, CH*H*), 5.30* (d, *J*= 16.8 Hz, 0.3H, C*H*H), 5.39* (d, J= 16.8 Hz, 0.3H, CH*H*), 6.24-6.29 (m, 1H, CH and CH*), 6.39 (d, *J*= 7.8 Hz, 0.7H, H-3′), 6.45 (dd, *J*= 3.0, 0.9 Hz, 0.7H, H-3), 6.52-6.54 (m with prominent d, *J*= 3.3 Hz, 1H, H-2 and H-3′*), 6.60 (d, *J*= 3.3 Hz, 0.3H, H-3*), 6.78 (d, *J*= 8.1 Hz, 1H, Ar), 7.03-7.21 (m, 4H, H-5, H-2′′, H-6′′and Ar), 7.20-7.21 (m, 1H, H-4′and Ar), 7.27-7.42 (m, 5H, H-7, H-3′′, H-5′′ and Ar), 7.57 (dd, *J*= 7.5, 1.5 Hz, 0.7H, H-4), 7.69 (d, *J*= 7.5 Hz, 0.3H, H-4*); ^{13}C NMR ($CDCl_3$) δ -1.3 (CH_2I), -0.8* (CH_2I), 19.1 (CH_3), 46.2 (CH_2), 55.7 (CH), 102.5 (C-3), 103.0* (C-3), 109.5, 119.9, 121.2, 122.0, 128.1, 128.2 (C-3a), 128.3, 128.5, 128.8, 128.89, 128.9, 129.5, 130.1, 135.6 (C-1′), 136.5 (C-7a), 138.0 (C-1′′), 139.2 (C-2′), 167.9 (CO); CI-MS *m/z* 495 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{24}N_2OI$: 495.0933, found: 495.0926.

Synthesis of *N*-ethoxycarbonyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl}iodoacetamide (182)



Following the procedure for **174**, treatment of **169** (32 mg, 0.091 mmol) with NaI (0.15 g, 0.94 mmol) in refluxing acetonitrile (3 mL) gave the title compound **182** (after purification by column chromatography with DCM; 27 mg, 66%) as a yellow solid; mp 53-54 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, *J*= 7.2 Hz, 3H, CH_3), 4.09 (ddd, *J*= 7.2, 6.9, 6.9 Hz, 1H, C*H*HCH$_3$), 4.20 (ddd, *J*= 7.2, 6.9, 6.9 Hz, 1H, CH*H*CH$_3$), 4.48 (dd, *J*= 9.6, 0.6 Hz, 1H, C*H*HI), 4.63 (dd, *J*= 9.3, 0.6 Hz, 1H, CH*H*I), 5.18 (d, *J*= 16.2 Hz, 1H, C*H*H), 5.25 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.56 (d, *J*= 3.3 Hz, 1H, H-3), 6.83 (d, *J*= 7.5 Hz, 1H, H-3′), 7.09 (d, *J*= 3.0 Hz, 1H, H-2), 7.11-7.17 (m, 4H, H-5, H-6, H-7, and H-6′), 7.26 (t, *J*= 7.2 Hz, 1H, H-4′), 7.34 (td, *J*= 7.5, 1.2 Hz, 1H, H-5′), 7.65 (dd, *J*= 6.9, 1.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 0.9 (CH_2I), 14.4 (CH_3), 46.6 (CH_2), 64.3 (*C*H$_2$CH$_3$), 102.2 (C-3), 109.9 (C-7), 119.9 (C-5), 121.2 (C-4), 122.0 (C-6), 128.2 (C-3′), 128.4 (C-6′), 128.7 (C-2), 128.9 (C-4′), 128.7 (C-3a), 129.5 (C-5′), 135.6 (C-1′), 135.7 (C-7a), 136.5 (C-2′), 153.1 (COO), 170.3 (CO); CI-MS *m/z* 463 ([M+H]$^{+}$, 15%); HREI-MS *m/z* calcd for $C_{21}H_{19}N_2O_3I$: 462.0440, found: 462.0445.

Synthesis of *N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]phenyl}-*N*-methyliodoacetamide (183)

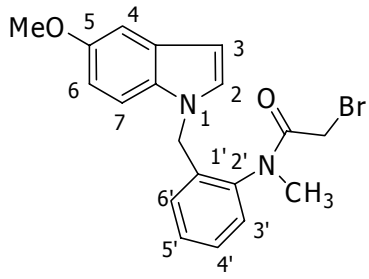


A suspension of NaH (18.2 mg, *ca* 50% dispersion in mineral oil, 0.38 mmol) in dry DMF (5 mL) under a N_2 atmosphere was cooled to 0-5 ^{o}C and a solution of **162** (0.11 g, 0.35 mmol) in DMF (15 mL) was then added dropwise. The mixture was then stirred for 30 min at r.t.. A solution of methyl iodide (54 μL, 0.87 mmol) in DMF (2 mL) was added and the reaction mixture

was stirred for a further 16 h. at r.t.. The solvent was evaporated, DCM (20 mL) was added and the organic layer washed with water (3 x 15 mL), dried and evaporated. The crude product was subjected to flash column chromatography (silica gel, DCM) to give **183** (0.076 g, 66%) as a yellow solid; mp 74-76 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.17 (s, 3H, CH_3), 3.29 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.43 (d, *J*= 10.2 Hz, 1H, CH*H*I), 5.29 (d, *J*= 16.5 Hz, 1H, C*H*H), 5.39 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.53 (dd, *J*= 3.9, 0.9 Hz, 1H, H-3), 6.91 (dd, *J*= 9.3, 2.7 Hz, 1H, H-4), 6.95 (dd, *J*= 7.8, 2.1 Hz, 1H, H-3′), 7.12 (d, *J*= 3.3 Hz, 1H, H-2), 7.15 (dd, *J*= 7.2, 2.4 Hz, 1H, H-7), 7.29 (ddd, *J*= 9.6, 7.2, 2.4 Hz, 1H, H-6), 7.32 (dd, *J*= 7.8, 1.5 Hz, 1H, H-6′), 7.36-7.44 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ -3.2 (CH_2I), 37.6 (CH_3), 47.2 (CH_2), 102.7 (d, *J*= 4.6 Hz, C^{13}-F^{19}, C3-F), 106.2 (d, *J*= 23.5 Hz, C^{13}-F^{19}, C6-F), 110.3 (d, J= 9.5 Hz, C^{13}-F^{19}, C7-F), 110.8 (d, *J*= 26 Hz, C^{13}-F^{19}, C4-F), 128.7, 129.2 (d, *J*= 10.4 Hz, C^{13}-F^{19}, C3a-F), 129.6, 129.88, 129.93, 130.0, 133.1 (C-7a), 134.6 (C-1′′), 141.4 (C-2′), 158.7 (d, *J*= 225.0 Hz, C^{13}-F^{19}, C5-F), 168.4 (CO); CI-MS *m/z* 423 ([M+H]$^+$, 43%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{18}H_{17}N_2OFI$: 423.0369, found: 423.0336.

7.2.8 Preparation of bromoacetamides

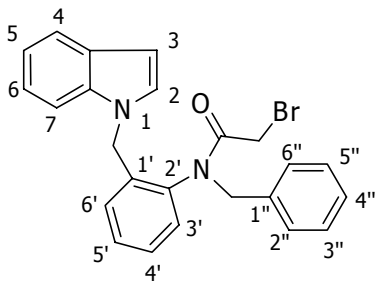
Synthesis of *N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}-*N*-methylbromo acetamide (184)



A mixture of **150b** (0.11 g, 0.41 mmol) and anhydrous K_2CO_3 (0.20 g, 1.50 mmol) in dry DCM (5 mL) was cooled to 0-5 ^{o}C and a solution of bromoacetyl chloride (80 µL, 1.03 mmol) in DCM (3 mL) was then added. Stirring was continued with cooling for a further 30 min and the reaction mixture then

allowed to warm to r.t. with stirring overnight. Distilled water (15 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried and concentrated to yield a yellow solid. The soild was subject to flash column chromatography (silica gel, DCM) to give **184** (83 mg, 54%) as yellow crystals; mp 58-59 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 3H, CH_3), 3.53 (d, *J*= 12.6 Hz, 1H, C*H*HBr), 3.63 (d, *J*= 12.6 Hz, 1H, CH*H*Br), 3.84 (s, 3H, OCH_3), 5.25 (d, *J*= 5.4 Hz, 2H, CH_2), 6.49 (dd, *J*= 3.0, 0.6 Hz, 1H, H-3), 6.83 (dd, *J*= 9.0, 2.4 Hz, 1H, Ar), 6.97 (dd, *J*= 7.8, 2.1 Hz, 1H, Ar), 7.02-7.10 (m, 2H, H-2 and Ar), 7.20-7.40 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 37.5 (CH_3), 41.2 (CH_2Br), 47.1 (CH_2), 56.1 (OCH_3), 102.3 (C-3), 103.2, 110.5, 112.6, 128.9, 129.3 (C-3a), 129.7, 129.8, 129.9, 131.6 (ArC), 135.2 (C-7a), 140.6 (C-2′), 154.4 (*C*OCH_3), 166.8 (CO); CI-MS *m/z* 387 ($[M+H]^+$, 13%); HREI-MS *m/z* calcd for $[M]^+$ $C_{19}H_{19}N_2O_2{}^{79}Br$: 386.0630, found: 386.0624.

Synthesis of *N*-benzyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl}bromoacetamide (185)



Following the reaction procedure for **184**, treatment of **153** (0.11 g, 0.34 mmol) with NaH (*ca* 50% dispersion in mineral oil, 18 mg, 0.38 mmol) and bromoacetyl chloride (0.10 mL, 0.85 ml) in dry DMF (20 mL) gave **185** (0.10 g, 68%), after purification by column chromatography (silica gel, 1:1 hexane/DCM), as a yellow solid; mp 99-101 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.43 (d, *J*= 1.8 Hz, 2H, CH_2Br), 4.62 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.34 (d, *J*= 16.8 Hz, 1H, C*H*H), 5.06 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.17 (d, *J*= 16.8 Hz, 1H, CH*H*), 6.55 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.81 (m, 1H, Ar), 6.87 (d, *J*= 3.3 Hz, 1H, H-2), 6.98 (m, 1H, Ar), 7.07 (dd, *J*= 6.9, 0.9 Hz, 1H, H-7), 7.12 (ddd, *J*= 8.4, 7.2, 1.2 Hz, 1H, H-5), 7.18 (td, *J*= 8.5, 1.2 Hz, 1H, H-6), 7.23-7.28 (m, 4H, Ar), 7.30- 7.35

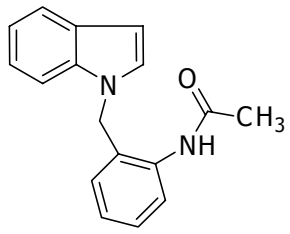
(m, 3H, Ar), 7.64 (dd, *J*= 8.0, 1.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 42.3 (CH_2Br), 46.7 (CH_2), 53.6 ($CONCH_2$), 102.7 (C-3), 109.3 (C-7), 120.1, 121.4, 122.3, 128.1, 128.4, 128.8 (C-3a), 129.0, 129.3, 129.4, 129.9, 130.1, 135.7 (ArC), 136.3 (ArC), 136.4 (C-2′), 138.9 (C-12a), 166.8 (CO); CI-MS *m/z* 433 ($[M+H]^+$, 90%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{21}N_2O^{79}Br$: 432.0837, found: 432.0851.

7.2.9 General procedure for radical cyclisation

A solution of tributyltin hydride (Bu_3SnH) (2.0 eq.) and AIBN (1.0 eq.) in an appropriate solvent (40 mM) was added dropwise to a solution of the haloacetamides (1.0 eq.) in boiling solvent (22 mM) over 4 h and the mixture was then heated at reflux overnight. After removing the solvent, diethyl ether (20 mL) and saturated potassium fluoride solution (20 mL) were added and the mixture was stirred vigorously at r.t. for 2-3 h. The organic layer was separated, dried and concentrated. The residue was column chromatographed on silica gel (hexane-AcOEt (3:1)).

Attempted cyclisation of 161

Following the general procedure, **161** (48 mg, 0.16 mmol) in toluene (5 mL) was treated with AIBN (26 mg, 0.16 mmol) and Bu_3SnH (86 μL, 0.32 mmol). The crude material was chromatographed (DCM) to give *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}acetamide **188a** (34 mg, 82%) as a yellow solid; mp 142-143 °C; ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 6.57 (d, *J*= 3.3 Hz, 1H, H-3), 6.73 (br s, 1H, NH), 7.02 (d, *J*= 3.3 Hz, 1H, H-2), 7.11-7.28 (m, 4H, Ar), 7.30-7.35 (m, 2H, H-4′ and Ar), 7.57 (d, *J*= 8.1 Hz, 1H, H-3′), 7.66 (d, *J*= 8.1 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 24.0 (CH_3), 47.9 (CH_2), 102.9 (C-3), 109.6 (C-7), 120.2,

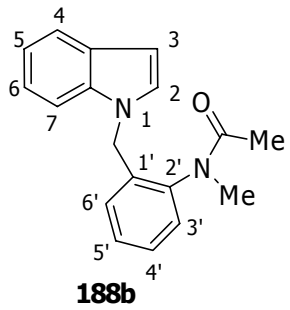


188a

121.5, 122.3, 125.5, 126.4, 127.8 (all ArCH), 128.9 (C-3a), 129.4 (ArCH), 130.5 (C-1′), 135.7 (C-7a), 136.4 (C-2′), 169.0 (CO); EI-MS *m/z* 264 ($[M]^+$, 90%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$: 265.1341, found: 265.1341.

Attempted cyclisation of 163

Following the general procedure, **163** (62 mg, 0.20 mmol) in toluene (5 mL) was treated with AIBN (33 mg, 0.20 mmol) and Bu_3SnH (0.11 mL, 0.40 mmol). The crude material was chromatographed (DCM) to give *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-methylacetamide **188b** (46 mg, 83%) as a yellow solid; mp 58-59 ^oC; ^1H NMR ($CDCl_3$) δ 1.78 (s, 3H, CH_3), 3.20 (s, 3H, NCH_3), 5.26 (s, 2H, CH_2-8), 6.58 (d, *J*= 3.0 Hz, 1H, H-3), 6.90 (d, *J*= 7.5 Hz, 1H, Ar), 7.07 (dd, *J*= 3.0, 0.6 Hz, 1H, H-2), 7.11-7.20 (m, 4H, Ar), 7.25 (t, *J*= 7.5 Hz, 1H, Ar), 7.35 (t, *J*= 7.5 Hz, 1H, Ar), 7.66 (dd, *J*= 7.8, 1.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_3), 36.6 (NCH_3), 46.6 (CH_2), 102.6, 109.7, 120.1, 121.2, 122.0, 128.2, 128.4, 129.0, 129.4, 135.0 (ArC), 136.3 (ArC), 140.1 (C-2′), 171.7 (CO); CI-MS *m/z* 279 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{18}H_{19}N_2O$: 279.1497, found: 279.1499.



188b

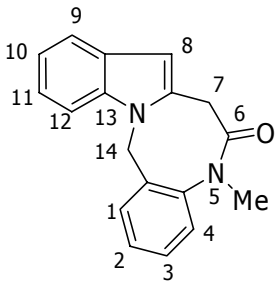
Attempted cyclisation of 174

Following the general procedure, **174** (0.10 g 0.21 mmol) in toluene (5 mL) was treated with AIBN (35 mg, 0.21 mmol) and Bu_3SnH (0.11 mL, 0.42 mmol). The crude material was chromatographed (DCM) to give **188a** (48 mg, 85%).

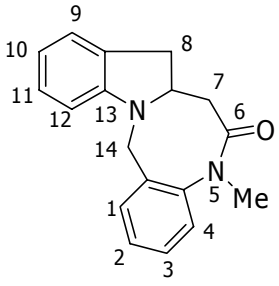
Cyclisation of 175 in Toluene

Following the general procedure, **175** (54 mg, 0.13 mmol) in toluene (5 mL) was treated with AIBN (21 mg, 0.13 mmol) and Bu_3SnH (70 μL, 0.26 mmol). The crude material was column chromatographed (DCM).

The first fraction from the column gave 5,14-dihydro-5-methyl-indolo[2,1-*d*][1,5]benzodiazocin-6-one **186b** (7 mg, 20%) as a yellow solid; mp 211-212 ^{o}C (from DCM); IR (KBr) ν_{max}: 2852 (N-CH_3), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.436 (s, 3H, CH_3), 3.447 (d, *J*= 13.8 Hz, 1H, C*H*H-7), 3.67 (d, *J*= 13.8 Hz, 1H, C*H*H-7), 4.75 (d, *J*= 14.1 Hz, 1H, C*H*H-14), 5.36 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 6.37 (s, 1H, H-8), 7.10 (t, *J*= 7.5 Hz, 1H, H-10), 7.23 (td, *J*= 8,1 Hz, 1H, Ar), 7.38 (d, *J*= 7.2 Hz, 1H, Ar), 7.46-7.56 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 36.2 (CH_2-7), 36.7 (NCH_3), 45.2 (CH_2-14), 103.6 (C-8), 108.7, 119.9, 120.6, 121.7, 125.5, 128.0 (C-8a), 129.0, 130.6, 131.8 (C-7a), 132.2, 133.0 (C-14a), 136.8 (C-12a), 144.7 (C-4a), 168.9 (CO); CI-MS *m/z* 277 ([M+H]$^{+}$, 100%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{18}H_{17}N_2O$: 277.1341, found: 277.1341.



The second fraction gave 5,7a,8,14-tetrahydro-5-methyl-indolo[2,1-*d*][1,5] benzodiazocin-6-one **187b**, (22 mg, 60%) as a yellow solid; mp 129-130 ^{o}C (from DCM);



^{1}H NMR ($CDCl_3$) δ 2.39-2.50 (m, 2H, CH_2-8), 2.60 (dd, *J*= 15.9, 9.0 Hz, 1H, C*H*H-7), 3.29 (dd, *J*= 15.9, 9.0 Hz, 1H, CH*H*-7), 3.38 (s, 3H, CH_3), 3.84 (d, *J*= 14.7 Hz, 1H, C*H*H-14), 4.08 (qd, *J*= 8.1, 1.2 Hz, 1H, H-7a), 4.55 (d, *J*= 15.0, 1H, CH*H*-14), 6.58 (*t*, *J*= 7.5 Hz, 1H, H-10), 6.68 (d, *J*= 7.8 Hz, 1H, H-12), 6.99 (d, *J*= 7.2 Hz, 1H, Ar), 7.06 (m, 2H, Ar), 7.22-7.39 (m, 3H, Ar), 7.52 (d, *J*= 7.2 Hz, 1H, H-9); ^{13}C NMR ($CDCl_3$) δ 36.8 (CH_2-7), 38.0 (CH_3), 42.7 (CH_2-8), 45.8 (CH_2-14), 62.4 (CH), 105.1 (C-12), 116.9, 124.8, 126.0, 127.6, 127.7 (C-8a), 128.3, 129.2, 131.6, 135.3 (ArC), 142.4 (ArC), 149.5 (C-4a), 172.1 (CO); CI-MS *m/z* 279 ([M+H]$^{+}$, 100%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{18}H_{18}N_2O$: 278.1419, found: 278.1413.

The third fraction gave **188b** (7 mg, 20%) as a yellow solid.

Cyclisation of 175 in Toluene on a larger scale

Following the general procedure, **175** (0.15 g, 0.36 mmol) in toluene (15 mL) was treacted with AIBN (58 mg, 0.36 mmol) and Bu_3SnH (1.94 ml, 0.72 mmol). The crude material was column chromatographed (DCM) to give **186b** (20 mg, 20%), **187b** (60 mg, 60%) and **188b** (20 mg, 20%).

Cyclisation of 175 in Mesitylene

Following the general procedure, **175** (56 mg, 0.14 mmol) in mesitylene (5 mL) was treated with AIBN (23 mg, 0.14 mmol) and Bu_3SnH (75 μL, 0.28 mmol). The crude material was column chromatographed (DCM) to give **186b** (17 mg, 44%).

Cyclisation of 175 using EPHP

A solution of **175** (40 mg, 0.10 mmol) and EPHP (0.23 g, 1.3 mmol) in dry benzene (5 mL) was heated at reflux for 1 h and a solution of AIBN (9 mg, 0.05 mmol) in benzene (10 mL) was added. The reaction mixture was then heated at reflux overnight and the solvent was evaporated. DCM (15 mL) was then added and the mixture was washed with water (3 x 15 mL). The DCM layer was separated, dried and concentrated and the residue was purified by flash column chromatography (silica gel; DCM). The first fraction from the column gave **186b** (2 mg, 9%) and the second fraction gave **188b** (9 mg, 33%).

Cyclisation of 176 using Bu_3SnH

Following the general procedure, **176** (83 mg, 0.19 mmol) in toluene (5 mL) was treated with AIBN (31 mg, 0.19 mmol) and Bu_3SnH (0.12 mL, 0.38 mmol). The crude material was column chromatographed (DCM).

The first fraction gave 5,14-dihydro-10-methoxy-5-methyl-indolo[2,1-*d*][1,5]benzodiazocin-6-one, **186c** (30 mg, 51%) as a yellow solid; mp 170-173 ^{o}C (DCM); ^{1}H NMR ($CDCl_3$) δ 3.430 (dd, *J*= 13.8, 1.2 Hz, 1H, C*H*H-7), 3.434 (s, 3H, CH_3), 3.63 (d, *J*= 13.5 Hz, 1H, CH*H*-7), 3.84 (s, 3H, OCH_3), 4.74 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 5.27 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 6.30 (s, 1H, H-3), 6.90 (dd, *J*= 9.0, 2.4 Hz, 1H, H-4), 7.01 (d, *J*= 2.4 Hz, 1H, H-9), 7.35-7.39 (m, 3H, Ar), 7.45- 7.53 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 36.1 (CH_2-7), 36.5 (NCH_3), 45.3 (CH_2-14), 56.1 (OCH_3), 102.4 (C-8), 103.2 (C-9), 109.4, 111.7, 125.4, 128.4 (C-8a), 129.0, 130.6, 131.8 (C-7a), 132.2, 133.1 (C-14a), 133.5 (C-12a), 144.8 (C-4a), 154.3 (*C*OCH_3), 168.9 (CO); CI-MS *m/z* 307 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{19}H_{19}N_2O_2$: 307.1447, found: 307.1444.

The second fraction gave *N*-{2-[1-(5-methoxy-1*H*-indolyl)methyl]phenyl}-*N*-methylacetamide **188c** (11 mg, 20%) as a yellow solid; mp 151-153 ^{o}C (DCM);

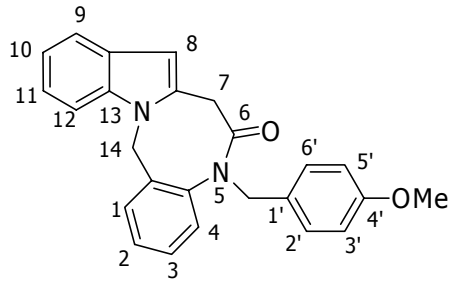
^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H, CH_3), 3.19 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 6.47 (d, *J*= 3.0 Hz, 1H, H-3), 6.80 (dd, *J*= 8.7, 2.1 Hz, 1H, Ar), 6.87 (d, *J*= 7.2 Hz, 1H, Ar), 6.98-7.07 (m with prominent d, *J*= 3.6 Hz, 2H, H-2 and Ar), 7.08 (d, *J*= 2.1 Hz, 1H, H-4), 7.10 (d, *J*= 7.8 Hz, 1H, Ar), 7.23 (t, *J*= 8.7 Hz, 1H, Ar), 7.32 (dd, *J*= 7.2, 0.9 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_3), 36.5 (NCH_3), 46.8 (CH_2), 56.0 (OCH_3), 102.0 (C-3), 103.0, 110.3, 112.5, 128.7, 129.1, 129.16, 129.24, 129.4, 129.7, 131.7 (ArC), 135.1 (ArC), 142.3 (C-2′), 154.5 (*C*OCH_3), 170.9 (CO); CI-MS *m/z* 309 ($[M+H]^+$, 87%); HREI-MS *m/z* calcd for $[M]^+$ $C_{19}H_{20}N_2O_2$: 308.1525, found: 308.1524.

Cyclisation of 176 using $(TMS)_3SiH$

A solution of $(TMS)_3SiH$ (92 μL, 0.30 mmol) and AIBN (32 mg, 0.20 mmol) in dry toluene (15 mL) was slowly added to a boiling solution of **176** (85 mg, 0.20 mmol) in dry toluene (35 mL) under a N_2 atmosphere. The solution was heated at reflux overnight and the solvent was then evaporated to leave a yellow residue which was purified by column chromatography using 2:3 EtOAc/hexane as an eluent. The first fraction from the column gave **186c** (6 mg, 10%) and the second fraction gave **188c** (22 mg, 36%).

Cyclisation of 177

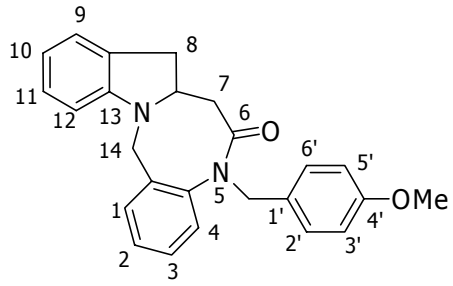
Following the general procedure, **177** (0.17 g, 0.33 mmol) in toluene (5 mL) was treated with AIBN (37 mg, 0.23 mmol) and Bu_3SnH (0.12 mL, 0.46 mmol). The crude material was column chromatographed (DCM).



The first fraction gave 5,14-dihydro-5-(4-methoxybenzyl)indolo[2,1-*d*][1,5]benzodiazocin-6-one **186d** (16 mg, 13%) as a yellow solid; mp 213-215 ^oC (DCM); ^1H NMR ($CDCl_3$) δ 3.42 (dd, *J*= 14.1, 1.2 Hz, 1H, C*H*H-7), 3.68 (d, *J*= 14.1 Hz, 1H, CH*H*-7), 3.76 (s, 3H, OCH_3), 4.10 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 4.50 (d, *J*= 13.8 Hz, 1H, CONC*H*H), 4.93 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 5.52 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 6.35 (s, 1H, H-8), 6.74 (d, *J*= 8.7 Hz, 2H, H-3′ and H-5′), 7.06 (t, *J*= 7.5 Hz, 1H, H-10), 7.11 (d, *J*= 8.7 Hz, 2H, H-2′ and H-6′), 7.18 (td, *J*= 7.2, 0.6 Hz, 1H, H-11), 7.30-7.40 (m, 4H, Ar), 7.46 (dd, *J*= 7.2, 1.5 Hz, 1H, Ar), 7.51 (d, *J*= 7.8 Hz, 1H, H-9); ^{13}C NMR ($CDCl_3$) δ 36.6 (CH_2-7), 44.8 (CH_2-14), 52.2 (CON*C*H_2), 55.5 (OCH_3), 103.5 (C-8), 108.7, 114.0, 119.8, 120.5, 121.5, 126.0, 128.0 (ArC), 128.5 (ArC), 129.0, 130.4, 130.9, 132.8 (ArC), 133.1 (ArC), 137.5 (C-12a), 142.8 (C-1′), 159.3 (*C*OCH_3),

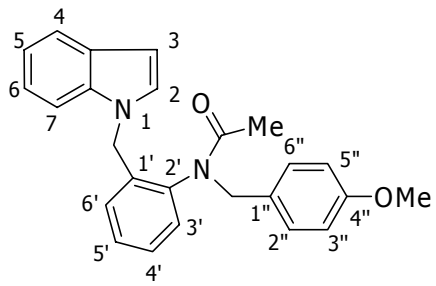
168.2 (CO); CI-MS *m/z* 383 ($[M+H]^+$, 100%); HRES-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{23}N_2O_2$: 383.1763, found: 383.1760.

The second fraction gave 5,7a,8,14-tetrahydro-5-(4-methoxybenzyl)indolo[2,1-*d*][1,5]benzodiazocin-6-one **187d** (13 mg, 11%) as a yellow solid; mp 107-109 ^oC (DCM);



^1H NMR ($CDCl_3$) δ 2.39-2.51 (m, 2H, CH_2-8), 2.56 (dd, *J*= 15.6, 8.4 Hz, 1H, C*H*H-7), 3.20-3.29 (m with prominent d, *J*= 14.1 Hz, 2H, CH*H*-7 and CONC*H*H), 3.76 (d, J= 1.2 Hz, 3H, OCH_3), 4.01 (q, *J*= 8.4 Hz, 1H, H-7a), 4.14 (d, *J*= 15.0 Hz, 1H, CONCH*H*), 4.38 (d, *J*= 14.1 Hz, 1H, C*H*H-14), 5.51 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 6.51-6.56 (m with prominent d, *J*= 6.9 Hz, 2H, Ar), 6.75 (d, *J*= 7.8 Hz, 2H, H-3′ and H-5′), 6.95 (d, *J*= 7.5 Hz, 1H, Ar), 7.04 (t, *J*= 8.4 Hz, 1H, Ar), 7.07 (d, *J*= 7.8 Hz, 2H, H-2′ and H-6′), 7.22-7.35 (m, 3H, Ar), 7.39 (d, *J*= 7.5 Hz, 1H, H-9); ^{13}C NMR ($CDCl_3$) δ 36.7 (CH_2-7), 42.6 (CH_2-8), 45.6 (CH_2-14), 53.1 (CON*C*H_2), 55.5 (OCH_3), 62.8 (CH), 105.0, 113.9, 116.7, 124.7, 126.7, 127.5, 127.7 (ArC), 128.4, 128.9 (ArC), 129.0, 130.7, 131.3, 136.7 (ArC), 140.4 (ArC), 154.7 (*C*OCH_3), 171.5 (CO); CI-MS *m/z* 385 ($[M+H]^+$, 100%); HRES-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{25}N_2O_2$: 385.1910, found: 385.1916.

The third fraction gave *N*-{2-[1-(1*H*-indolyl)methyl]phenyl}-*N*-(4-methoxy benzyl)acetamide **188d** (9 mg, 7%) as a yellow solid; mp 58-60 ^oC (DCM);

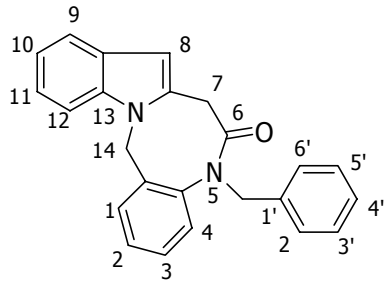


^1H NMR ($CDCl_3$) δ 1.81 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.75 (d, *J*= 15.9 Hz, 2H, C*H*H and CONC*H*H), 4.84 (d, *J*= 13.8 Hz, 1H, CH*H*), 5.03

(d, *J*= 17.2 Hz, 1H, CONCH*H*), 6.53 (dd, *J*= 3.0, 1.5 Hz, 1H, H-3), 6.65 (d, *J*= 7.8 Hz, 1H, H-3′), 6.83 (m with prominent dd, *J*= 8.7, 2.4 Hz, 3H, H-2, H-3′′ and H-5′′), 6.95 (t, *J*= 8.7 Hz, 1H, H-5′), 7.08-7.17 (m, 3H, H-2′′, H-6′′ and Ar), 7.20-7.23 (m, 2H, Ar), 7.42-7.52 (m, 2H, Ar), 7.63 (d, *J*= 6.9 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 22.5 (CH_3), 47.4 (CH_2), 52.1 (CON*C*H_2), 55.5 (OCH_3), 102.5 (C-3), 109.5, 114.2, 111.9, 121.3, 122.1, 128.3, 128.5, 129.2, 129.7, 130.9, 131.3, 132.4 (ArC), 135.9 (ArC), 137.6 (C-1′′), 140.3 (C-2′), 159.6 (*C*OCH_3), 168.2 (CO); CI-MS *m/z* 385 ($[M+H]^+$, 100%); HRES-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{25}N_2O_2$: 385.1910, found: 385.1916.

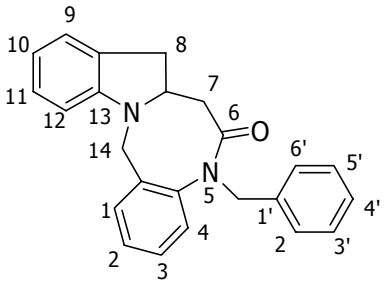
Cyclisation of 178 in toluene

Following the general procedure, **178** (38 mg, 0.08 mmol) in toluene (5 mL) was treated with AIBN (13 mg, 0.08 mmol) and Bu_3SnH (43 μL, 0.16 mmol). The crude material was column chromatographed (DCM). The first fraction from the column gave 5-benzyl-5,14-dihydroindolo[2,1-*d*][1,5]benzodiazocin-6-one **186e** (8 mg, 25%) as a yellow solid; mp 154-155 °C (DCM); IR (KBr) ν_{max}: 1661 (C=O) cm^{-1};



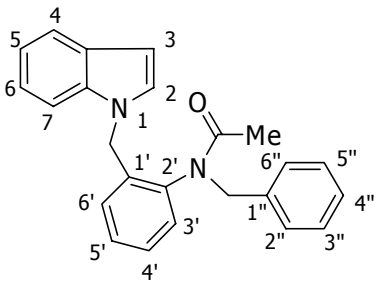
^{1}H NMR ($CDCl_3$) δ 3.45 (dd, *J*= 13.8, 1.5 Hz, 1H, C*H*H-7), 3.71 (d, *J*= 13.8 Hz, 1H, CH*H*-7), 4.13 (d, *J*= 14.1 Hz, 1H, CONC*H*H), 4.62 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 4.93 (d, *J*= 13.8 Hz, 1H, CONCH*H*), 5.53 (d, *J*= 14.1 Hz, 1H, CH*H*-14), 6.37 (s, 1H, H-8), 7.07 (t, *J*= 7.8, 1.2 Hz, 1H, H-10), 7.16-7.25 (m, 7H, Ar), 7.34 (d, *J*= 7.8 Hz, 1H, Ar), 7.38-7.42 (m, 2H, Ar), 7.46 (dd, *J*= 8.1, 1.8 Hz, 1H, Ar), 7.52 (d, *J*= 7.8 Hz, 1H, H-9); ^{13}C NMR ($CDCl_3$) δ 36.6 (CH_2-7), 44.8 (CH_2-14), 52.8 (CON*C*H_2), 103.6 (C-8), 108.7, 119.8, 120.5, 121.5, 125.9, 128.0 (C-8a), 128.2, 128.8, 129.0, 129.6, 130.5, 132.1, 132.7 (C-7a), 133.0 (C-14a), 136.3 (C-

12a), 137.5 (C-1′), 142.8 (C-4a), 168.4 (CO); CI-MS *m/z* 353 ([M+H]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$ $C_{24}H_{20}N_2O$: 352.1576, found: 352.1565.



The second fraction gave 5-benzyl-5,7a,8,14-tetrahydroindolo[2,1-*d*][1,5] benzodiazocin-6-one **187e** (12 mg, 43%) as a yellow solid; mp 141-144 ^oC (DCM); IR (KBr) ν_{max}: 1647 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41- 2.52 (m, 2H, CH_2-8), 2.57 (dd, *J*= 15.9, 9.3 Hz, 1H, C*H*H-7), 3.22- 3.30 (m with prominent d, *J*= 15.3 Hz, 2H, CH*H*-7 and CONC*H*H), 4.02 (qd, *J*= 9.0, 1.2 Hz, 1H, H-7a), 4.14 (d, *J*= 15.0 Hz, 1H, CONCH*H*), 4.50 (d, *J*= 14.1 Hz, 1H, C*H*H-14), 5.51 (d , *J*= 14.1 Hz, 1H, CH*H*-14), 6.51- 6.56 (m, 2H, Ar), 6.95 (d, *J*= 6.9 Hz, 1H, Ar), 7.04 (t, *J*= 7.8 Hz, 1H, Ar), 7.14- 7.19 (m, 2H, Ar), 7.22-7.27 (m, 5H, Ar), 7.30 (dd, *J*= 9.0, 1.8 Hz, 1H, Ar), 7.40 (dd, *J*= 9.0, 2.4 Hz, 1H, H-9); ^{13}C NMR ($CDCl_3$) δ 36.6 (CH_2-7), 42.5 (CH_2-8), 45.5 (CH_2-14), 53.7 (CONCH_2), 62.7 (CH-7), 105.0, 116.8, 124.8, 126.7, 127.6, 127.7 (C-8a), 128.0, 128.5, 128.7, 129.1, 129.4, 131.4 (ArC), 136.7 (ArC), 136.8 (C-1′), 149.6 (C-4a), 171.1 (CO); CI-MS *m/z* 355 ([M+H]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$ $C_{24}H_{22}N_2O$: 354.1732, found: 354.1718.

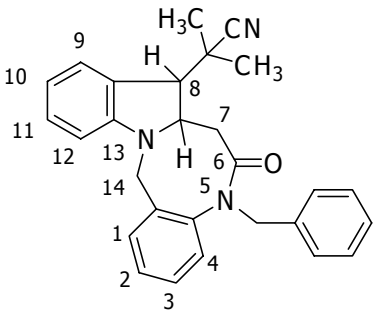
The third fraction gave *N*-benzyl-*N*-{2-[1-(1*H*-indolyl)methyl]phenyl}acetamide **188e** (3 mg, 10%) as a yellow solid; mp 158-159 ^oC (DCM); IR (KBr) ν_{max}: 1676 (C=O), 1358 (CO-CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H, CH_3), 4.74 (d, *J*= 16.8, 1H, CONC*H*H), 4.80 (d, *J*= 14.1 Hz, 1H, C*H*H), 4.92 (d, *J*= 14.1 Hz, 1H, CH*H*), 5.04 (d, *J*= 16.8 Hz, 1H, CONCH*H*), 6.53 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.65 (d, *J*= 7.8 Hz, 1H, H-3′), 6.79 (d, *J*= 3.3 Hz, 1H, H-2), 6.94- 6.99 (m, 2H, Ar), 7.11 (td, *J*= 7.2, 1.2 Hz, 1H, Ar), 7.15-7.16 (m, 2H, H-5 and H-5′), 7.21



(td, *J*= 8.4, 1.8 Hz, 1H, H-4′), 7.24- 7.29 (m, 3H, Ar), 7.30- 7.35 (m, 2H, Ar), 7.64 (ddd, *J*= 7.2, 1.8, 0.6 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 22.6 (CH_3), 46.4 (CH_2), 52.7 (CON*C*H_2), 102.5 (C-3), 109.6, 120.0, 121.3, 122.1, 128.4, 128.5, 128.8 (C-3a), 128.9, 129.2, 129.7, 129.8, 135.9 (C-1′), 136.5 (C-7a), 137.2 (C-1′′), 140.3 (C-2′), 170.6 (CO); CI-MS *m/z* 355 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{22}N_2O$: 354.1732, found: 354.1732.

Cyclisation of 178 on a larger scale

Compound **178** (0.30 g, 0.68 mmol) in toluene (45 mL) was treated with AIBN (0.12 g, 0.72 mmol) and Bu_3SnH (0.39 mL, 1.44 mmol). The crude material was column chromatographed (DCM) to give **186e** (26 mg, 12%), **187e** (42.8 mg, 19%) and **188e** (70 mg, 32%). A further product from the chromatographic separation was compound **189** (10 mg, 4%), obtained as a yellow solid; mp 76-77 ^{o}C; IR (KBr) ν_{max}: 1650 (C=O) cm^{-1};



^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H ,CH_3), 1.49 (s, 3H, CH_3), 2.21 (d, *J*= 12.3 Hz, 1H, C*H*H-7), 2.58 (dd, *J*= 12.3, 10.5 Hz, 1H, CH*H*-7), 3.01 (d, *J*= 3.3 Hz, 1H, H-8), 3.43 (d, *J*= 15.6 Hz, 1H, C*H*H-14), 3.96 (dd, *J*= 10.5, 3.6 Hz, 1H, H-7a), 4.24 (d, *J*= 15.6 Hz, 1H, CH*H*-14), 4.56 (d, *J*= 13.5 Hz, 1H, CONC*H*H), 5.44 (d, *J*= 13.5 Hz, 1H, CONCH*H*), 6.58 (t, *J*= 7.2 Hz, 1H, H-10), 6.65 (d, *J*= 8.1 Hz, 1H, H-12), 7.12-7.20 (m, 3H, H-2, H-11 and Ar), 7.22-7.29 (m, 5H, Ar), 7.30-7.34 (m, 2H, H-9 and Ar), 7.47 (d, *J*= 7.5 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 21.9 (CH_3), 24.5 (CH_3), 36.7 (*C*CN), 44.2 (CH_2-7), 44.3 (CH_2-14), 53.6 (CON*C*H_2), 56.1 (C-8), 63.5 (C-7a), 106.8 (C-7), 116.8 (C-5), 124.7 (CN), 125.4 (C-8a), 126.2 (C-4), 126.6, 128.0, 128.1, 128.7 (all ArCH), 129.2 (C-11), 129.37, 129.4 (all ArCH), 132.0 (C-1), 135.3 (C-14a), 136.6 (C-1′), 140.7 (C-4a), 149.1 (C-12a),

171.1 (CO); CI-MS *m/z* 422 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{28}H_{27}N_3O$: 421.2154, found: 421.2160.

Cyclisation of 178 in xylene

Following the general procedure, **178** (52 mg, 0.11 mmol) in xylene (5 mL) was treated with AIBN (18 mg, 0.11 mmol) and Bu_3SnH (59 μL, 0.22 mmol). The crude material was column chromatographed (DCM) to give **186e** (22 mg, 57%).

Cyclisation of 178 in mesitylene

Following the general procedure, **178** (51 mg, 0.11 mmol) in mesitylene (5 mL) was treated with AIBN (18 mg, 0.11 mmol) and Bu_3SnH (59 μL, 0.22 mmol). The crude material was column chromatographed (DCM) to give **186e** (27 mg, 70%).

Cyclisation of 178 in *tert*-butylbenzene

Following the general procedure, **178** (55mg, 0.12 mmol) in *tert*-butylbenzene (5 mL) was treated with AIBN (20 mg, 0.11 mmol) and Bu_3SnH (65 μL, 0.22 mmol). The crude material was column chromatographed (DCM) to give **186e** (19 mg, 46%) and **187e** (4 mg, 9%).

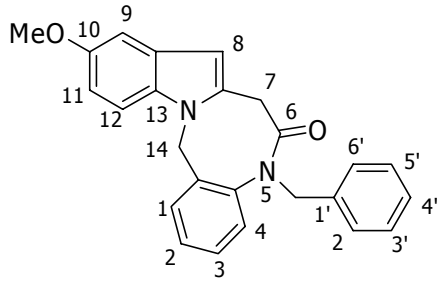
Cyclisation of 178 in toluene using $(TMS)_3SiH$

A solution of $(TMS)_3SiH$ (74 μL, 0.30 mmol) and AIBN (20 mg, 0.12 mmol) in dry toluene (25 mL) was slowly added to a boiling solution of **178** (55 mg, 0.12 mmol) in dry toluene (5 mL) under a N_2 atmosphere. The solution was heated at reflux overnight and the solvent was then evaporated to leave a yellow residue which was purified by PTLC (DCM). The higher R_f band gave **186e** (13 mg, 31%) and the lower R_f band gave **188e** (23 mg, 54%).

Cyclisation of 178 in xylenes using $(TMS)_3SiH$

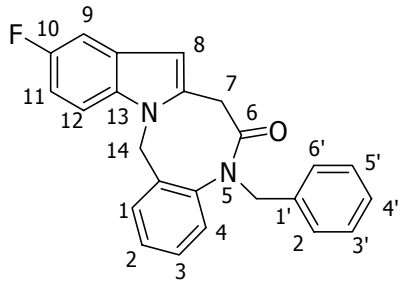
A solution of $(TMS)_3SiH$ (67 μL, 0.22 mmol) and AIBN (18 mg, 0.11 mmol) in dry xylenes (25 mL) was slowly added to a boiling solution of **178** (53 mg, 0.11 mmol) in dry xylenes (5 mL) under a N_2 atmosphere. The solution was heated at reflux overnight and the solvent was then evaporated to leave a yellow residue which was purified by PTLC (DCM). The first band (higher R_f) gave **186e** (3 mg, 9%) and the second band (lower R_f) gave **188e** (17 mg, 43%).

Cyclisation of 179

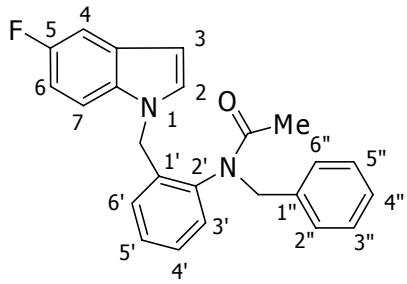


Following the general procedure, **179** (55 mg, 0.11 mmol) in mesitylene (5 mL) was treated with AIBN (18 mg, 0.11 mmol) and Bu_3SnH (59 μL, 0.22 mmol). The crude material was column chromatographed (0 to 100% DCM-hexane) to give 5-benzyl-5,14-dihydro-10-methoxyindolo[2,1-*d*][1,5]benzodiazocin-6-one **186f** (12 mg, 29%) as a yellow solid; mp 113-114 ^oC (DCM); ^1H NMR ($CDCl_3$) δ 3.42 (dd, *J*= 15, 1.2 Hz, 1H, C*H*H-7), 3.68 (d, *J*= 13.8 Hz, 1H, CH*H*-7), 3.82 (s, 3H, OCH_3), 4.12 (s, *J*= 13.8 Hz, 1H, CONC*H*H), 4.62 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 4.85 (d, *J*= 14.0 Hz, 1H, CONCH*H*), 5.51 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 6.28 (s, 1H, H-8), 6.84 (dd, *J*= 9.0, 2.4 Hz, 1H, H-4), 6.99 (d, *J*= 2.4 Hz, 1H, H-9), 7.21-7.25 (m, 6H, Ar), 7.31-7.50 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 36.4 (CH_2-7), 44.9 (CH_2-14), 52.7 (CON*C*H_2), 56.1 (OCH_3), 102.4 (C-8), 109.4, 111.6, 125.9, 128.2, 128.3 (C-8a), 128.8, 129.7, 129.6, 130.0, 130.5, 132.1, 132.7 (C-7a), 132.9 (C-14a), 133.5 (C-12a), 136.4 (C-1′), 142.9 (C-4a), 154.3 (*C*OCH_3), 168.4 (CO); CI-MS *m/z* 383 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{25}H_{23}N_2O_2$: 383.1760, found: 383.1766.

Cyclisation of 180



Following the general procedure, **180** (77 mg, 0.16 mmol) in mesitylene (7 mL) was treated with AIBN (25 mg, 0.16 mmol) and Bu_3SnH (77 μL, 0.31 mmol). The crude material was column chromatographed (0 to 100% DCM-hexane). The first fraction gave 5-benzyl-10-fluoro-5,14-dihydroindolo[2,1-*d*][1,5]benzodiazocin-6-one **186g** (14 mg, 23%) as a yellow solid; mp 115-116 ^{o}C (DCM); ^{1}H NMR ($CDCl_3$) δ 3.43 (dd, *J*= 13.8, 1.2 Hz, 1H, C*H*H-7), 3.69 (d, *J*= 13.8 Hz, 1H, CH*H*-7), 4.13 (d, *J*= 14.1 Hz, 1H, C*H*H-14), 4.63 (d, *J*= 14.1 Hz, 1H, CONC*H*H), 4.86 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 5.52 (d, *J*= 14.1 Hz, 1H, CONCH*H*), 6.31 (s, 1H, H-8), 6.90 (dd, *J*= 9.0, 2.7 Hz, 1H, Ar), 6.94 (dd, *J*= 9.0, 2.4 Hz, 1H, H-9), 7.16 (dd, *J*= 9.6, 2.4 Hz, 1H, H-12), 7.19-7.27 (m, 5H, Ar), 7.31-7.40 (m, 3H, Ar), 7.47 (dd, J= 6.6, 2.1 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 36.4 (CH_2-7), 45.0 (CH_2-14), 52.6 (CON*C*H_2), 105.5 (d, *J*= 4.6 Hz, C^{13}-F^{19}, C8-F), 105.3 (d, *J*= 23.5 Hz, C^{13}-F^{19}, C11-F), 109.3 (d, *J*= 9.8 Hz, C^{13}-F^{19}, C12-F), 109.7 (d, *J*= 26.3 Hz, C^{13}-F^{19}, C9-F), 126.0, 128.2, 129.2, 129.6, 130.1, 130.7, 132.1, 132.4 (ArC), 134.1 (ArC), 134.6 (ArC), 136.3 (C-1′), 142.8 (C-4a), 158.7 (d, *J*= 238.6 Hz, C^{13}-F^{19}, C10-F), 168.2 (CO); CI-MS *m/z* 371 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{24}H_{20}N_2O_2F$: 371.1560, found: 371.1552.

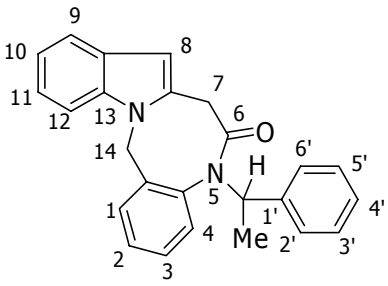


The second fraction gave *N*-benzyl-*N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]- phenyl}acetamide **188g** (9 mg, 15 %) as a yellow solid; mp 63-64 ^{o}C (DCM); ^{1}H NMR ($CDCl_3$) δ 1.80 (d, 3H, CH_3), 4.70 (d, *J* = 16.8 Hz, 1H, CONC*H*H), 4.84 (d, *J*= 5.1 Hz, 1H, CH_2-8), 5.00 (d, *J*= 16.8 Hz, 1H, CONCH*H*), 6.48 (dd, *J*= 2.7, 0.6 Hz, 1H, H-3), 6.63 (dd, *J*=

7.5, 1.2 Hz, 1H, H-12), 6.79 (m with prominent d, *J*= 3.3 Hz, 2H, H-2 and H-4), 6.88 (td, *J*= 9.0, 2.4 Hz, 1H, H-6), 6.97 (dd, *J*= 7.8, 1.5 Hz, 1H, H-9), 7.20 (td, *J*= 7.5, 1.5 Hz, 1H, Ar), 7.23-7.28 (m, 5H, Ar), 7.29-7.34 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_3), 46.4 (CH_2-8), 52.5 (CH_2-1′), 102.1 (d, *J*= 4.9 Hz, C^{13}-F^{19}, C3-F), 105.8 (d, *J*= 11.6 Hz, C^{13}-F^{19}, C7-F), 109.9 (d, J= 9.8 Hz, C^{13}-F^{19}, C6-F), 110.3 (d, J= 26.3 Hz, C^{13}-F^{19}, C4-F), 127.9, 128.2, 128.7, 128.9, 129.0, 129.2, 129.5, 129.67, 129.71, 135.4 (C-7a), 136.9 (C-8a), 140.1 (C-4a), 157.9 (d, *J*= 233.1 Hz, C^{13}-F^{19}, C5-F), 170.3 (CO); CI-MS *m/z* 373 $[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{24}H_{22}N_2O_2F$: 373.1716, found: 373.1704.

Cyclisation of 181

Following the general procedure, **181** (37 mg, 0.07 mmol) in toluene (5 mL) was treated with AIBN (12 mg, 0.07 mmol) and Bu_3SnH (40 μL, 0.15 mmol). The crude material was column chromatographed (DCM). The first fraction gave 5,14-dihydro-5-(1-phenylethyl)indolo[2,1-*d*][1,5]benzodiazocin-6-one **186h** (6 mg, 22%) as a yellow solid; mp 157-159 ^{o}C (DCM);



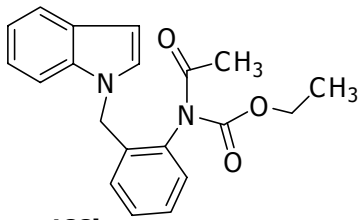
^{1}H NMR ($CDCl_3$, rotamer ratio 52:48*) δ 1.56 (d, *J*= 7.2 Hz, 1.6H, CHC*H*$_3$), 1.78* (d, *J*= 7.5 Hz, 1.4 Hz, CHC*H*$_3$), 3.33* (d, *J*= 13.8 Hz, 0.5 H, C*H*H-7), 3.38 (d, *J*= 12.3 Hz, 0.5 H, C*H*H-7), 3.66* (d, *J*= 13.5 Hz, 0.5 H, CH*H*-7), 3.72 (d, *J*= 14.1 Hz, 0.5 H, CH*H*-7), 3.73* (d, *J*= 13.8 Hz, 0.5H, C*H*H-14), 4.64* (d, *J*= 13.8 Hz, 0.5 H, CH*H*-14), 4.88 (d, *J*= 13.8 Hz, 0.5 H, C*H*H-14), 5.37 (d, J= 13.5 Hz, 0.5 H, CH*H*-14), 6.32* (br s, 0.5H, C*H*CH_3), 6.32* (s, 0.5 Hz, H-8), 6.35 (s, 0.5 Hz, H-8), 6.38 (br s, 0.5H, C*H*CH_3), 6.54 (d, *J*= 8.1 Hz, 0.5H, H-4), 7.02-7.56 (m, 12.5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3), 19.0* (CH_3), 36.9 (CH_2-7), 44.3* (CH_2-14), 45.2 (CH_2-14), 52.8* (CH), 53.9 (CH),

103.2* (C-8), 103.3 (C-8), 108.4 (C-15), 119.4*, 119.6, 120.2*, 120.3. 121.1*, 121.3, 127.0* (C-4), 127.7, 128.0, 128.1, 128.2, 128.5, 129.0, 129.4, 130.8 (C-3a), 131.7*, 131.8, 132.8 (C-7a), 133.0* (C-14a), 133.2* (C-7a), 134.2, (C-14a), 137.3* (C-12a), 138.9 (C-12a), 139.5 (C-1′), 140.3* (C-1′), 141.6 (C-4a), 145.5* (C-4a), 164.4 (CO), 168.4* (CO); CI-MS *m/z* 367 ($[M+H]^+$, 100%); HRCI-MS m/z calcd for $[M+H]^+$ $C_{25}H_{23}N_2O$: 367.1810, found: 367.1796.

Further fractions then gave a mixture of **187h** and **188h** (7 mg, 26%) in a ratio of *ca* 1:1 (determined by ^{1}H NMR spectroscopy).

Cyclisation of 182

Following the general procedure, **182** (23 mg, 0.06 mmol) in toluene (5 mL) was treated with AIBN (10 mg, 0.06 mmol) and Bu_3SnH (32 μL, 0.12 mmol). The crude material was column chromatographed (DCM). The first fraction gave the amine **149a** (4 mg, 34%), the second fraction gave *N*-ethoxycarbonyl-*N*-{2-[1-(1*H*-indolyl)methyl]-phenyl}acetamide **188i** (7 mg, 37%) as a yellow solid; mp 82-83 ^{o}C (DCM); ^{1}H NMR



188i

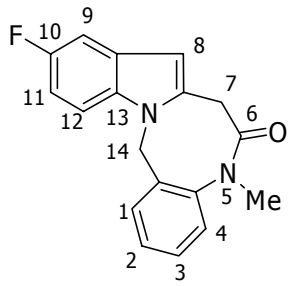
($CDCl_3$) δ 1.10 (td, *J*= 6.9, 0.6 Hz, 3H, CH_2CH_3), 2.64 (s, 3H, CH_3), 3.97 (ddd, *J*= 7.2, 7.2, 6.9 Hz, 1H, C*H*HCH$_3$), 4.06 (ddd, *J*= 7.2, 7.2, 6.9 Hz, 1H, CH*H*CH$_3$), 5.10 (d, *J*= 16.2 Hz, 1H, C*H*H), 5.18 (d, *J*= 16.2 Hz, 1H, CH*H*), 6.54 (d, *J*= 3.0 Hz, 1H, H-3), 6.88 (dd, *J*= 7.5, 1.5 Hz, 1H, H-3′), 7.05 (d, *J*= 3.0 Hz, 1H, H-2), 7.08-7.15 (m, 4H, Ar), 7.25 (td, *J*= 7.8, 1.5 Hz, 1H, H-4′), 7.32 (dd, *J*= 7.5, 1.5 Hz, 1H, Ar), 7.63 (dd, *J*= 6.3, 2.1 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_2CH_3), 26.9 (CH_3), 47.0 (CH_2), 63.6 (CH_2CH_3), 102.1 (C-3), 109.9 (C-7), 119.8 (C-5), 121.2 (C-4), 122.0 (C-6), 128.3 (C-2), 128.6 (C-3′), 128.86 (C-6′), 128.9 (C-3a), 129.0 (C-5′), 129.2 (C-4′), 135.1 (C-1′), 136.3 (C-7a), 136.5 (C-2′), 153.7

(COO), 172.8 (CO); EI-MS *m/z* 336 ($[M]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{20}H_{21}N_2O_3$: 337.1552, found: 337.1552.

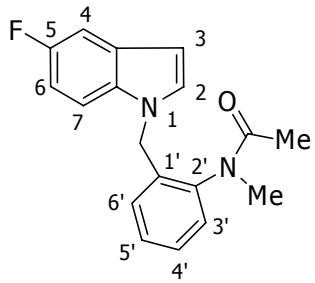
Cyclisation of 183

Following the general procedure, **183** (60 mg, 0.14 mmol) in toluene (5 mL) was treated with AIBN (23 mg, 0.14 mmol) and Bu_3SnH (75 μL, 0.28 mmol). The crude material was column chromatographed (DCM).

The first fraction gave 10-fluoro-5,14-dihydo-5-methyl-indolo[2,1-*d*][1,5] benzodiazocin-6-one **186j** (15 mg, 35%) as a yellow solid; mp 200-202 ^oC (DCM);



^1H NMR ($CDCl_3$) δ 3.436 (s, 3H, CH_3), 3.439 (d, *J*= 13.8 Hz, 1H, C*H*H-7), 3.65 (d, *J*= 14.1 Hz, 1H, CH*H*-7), 4.76 (d, *J*= 13.8 Hz, 1H, C*H*H-14), 5.29 (d, *J*= 13.8 Hz, 1H, CH*H*-14), 6.33 (s, 1H, H-8), 6.97 (td, *J*= 9.0, 2.7 Hz, 1H, H-11), 7.18 (dd, *J*= 9.3, 2.4 Hz, 1H, H-9), 7.35-7.40 (m, 3H, Ar), 7.48 (dd, *J*= 7.5, 1.8 Hz, 1H, Ar), 7.51 (d, *J*= 7.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 36.2 (CH_2-7), 36.7 (NCH_3), 45.5 (CH_2-14), 103.5 (d, *J*= 4.3 Hz, C^{13}-F^{19}, C8-F), 105.4 (d, *J*= 23.2 Hz, C^{13}-F^{19}, C11-F), 109.3 (d, *J*= 9.5 Hz, C^{13}-F^{19}, C12-F), 109.9 (d, *J*= 49.0 Hz, C^{13}-F^{19}, C9-F), 125.5, 128.2 (d, *J*= 10.1 Hz, C^{13}-F^{19}, C8a-F), 129.0, 130.7, 131.4 (C-7a), 132.1, 134.3 (C-14a), 134.6 (C-12a), 144.6 (C-4a), 158.0 (d, *J*= 232.7 Hz, C^{13}-F^{19}, C10-F), 168.6 (CO); CI-MS *m/z* 295 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{18}H_{15}N_2OF$: 294.1168, found: 294.1159.



The second fraction gave *N*-{2-[1-(5-fluoro-1*H*-indolyl)methyl]phenyl}-*N*-methylacetamide **188j** (7 mg, 17%) as a yellow solid; mp 70-72 ^oC (DCM);

^1H NMR ($CDCl_3$) δ 1.74 (s, 3H, CH_3), 3.17 (s, 3H, NCH_3), 5.23 (s, 2H, CH_2-8), 6.52 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.89-6.95 (m, 2H, Ar), 7.06 (dd,

J= 9.3, 4.5 Hz, 1H, H-4), 7.09 (d, *J*= 3.0 Hz, 1H, H-2), 7.18 (dd, *J*= 7.8, 1.5 Hz, 1H, Ar), 7.25-7.30 (m, 2H, Ar), 7.36 (dd, *J*= 7.5, 1.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 22.3 (CH_3), 36.7 (NCH_3), 47.1 (CH_2), 102.5 (d, *J*= 4.6 Hz, C^{13}-F^{19}, C3-F), 106.2 (d, *J*= 23.2 Hz, C^{13}-F^{19} , C6-F), 110.2 (d, *J*= 9.7 Hz, C^{13}-F^{19}, C7-F), 110.7 (d, *J*= 26.5 Hz, C^{13}-F^{19}, C4-F), 128.8, 128.9, 129.1, 129.2, 129.5 (d, *J*= 4.5 Hz, C^{13}-F^{19}, C3a-F), 129.9, 130.0, 133.0 (C-1′), 134.6 (C-7a), 142.4 (C-2′), 157.6 (d, *J*= 232.2 Hz, C^{13}-F^{19}, C5-F), 170.7 (CO); CI-MS *m/z* 297 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{18}H_{17}N_2OF$: 296.1325, found: 296.1320.

Cyclisation of 184

Following the general procedure, **184** (45 mg, 0.12 mmol) in toluene (5 mL) was treated with AIBN (20 mg, 0.12 mmol) and Bu_3SnH (64 μL, 0.24 mmol). The crude material was column chromatographed (DCM). The first fraction gave **186c** (9 mg, 24%) and the second fraction gave **188c** (12 mg, 33%).

Cyclisation of 185

Following the general procedure, **185** (44 mg, 0.10 mmol) in toluene (5 mL) was treated with AIBN (16 mg, 0.10 mmol) and Bu_3SnH (53 μL, 0.20 mmol). The crude material was column chromatographed (DCM) to give **186e** (19 mg, 54%) and in the second fraction, a mixture of **187e** and **188e** (7 mg, 20%) in a ratio of *ca* 2:1 (determined by ^{1}H NMR spectroscopy).

7.2.10 Dehydrogenation of 187b

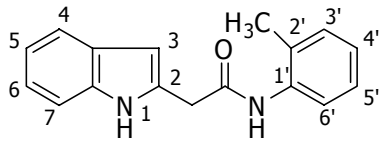
5,14-dihydro-5-methyl-indolo[2,1-*d*][1,5]benzodiazocin-6-one

To a solution of **187b** (98 mg, 0.35 mmol) in dry toluene (5 mL) was added 10% Pd/C (20 mg). The reaction mixture was then heated at reflux for 8 h. The mixture was then cooled, filtered through Celite and the filtrate evaporated to dryness. The crude yellow solid residue was column chromatographed (DCM) to yield **186b** (48 mg, 50%) and the starting material **187b** (40 mg, 40%).

7.2.11 Debenzylation

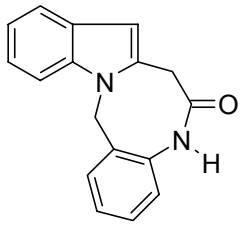
Debenzylation of 186e

Method A: Sodium metal (*ca* 30 mg) was added in dry THF under a N_2 atmosphere and then the mixture was cooled using liquid N_2 bath. Liquid ammonia (condensed at –70 ^{o}C, *ca* 7 mL) and a solution of **186e** (30 mg, 0.09 mmol) in dry THF (2 mL) was added. The frozen mixture was warmed to –60 ^{o}C and the reaction was stirred for 30 min. Solid ammonium chloride was added until the colour dissipated at which point the reaction was allowed to warm to r.t.. The residue was dissolved in ethyl acetate (30 mL), extracted with water (20 mL), dried and concentrated to give a yellow residue. The residue was purified using preparative thin layer chromatography (silica gel, 1% MeOH/DCM) to give two major bands.



The first band (higher R_f) gave 2-(1*H*-indol-2yl)-*N*-*o*-tolylacetamide **190** (3.3 mg, 14%) as a yellow solid; mp 131-133 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 6.48 (s, 1H, H-3), 7.05-7.21 (m, 5H, Ar), 7.34 (dd, *J*= 7.5, 0.9 Hz, 1H, H-7), 7.36 (br s, 1H, indole NH), 7.59 (d, *J*= 7.8 Hz, 1H, Ar), 7.78 (d, *J*= 8.1 Hz, 1H, H-6′), 8.82 (br s, 1H, NH); ^{13}C

NMR ($CDCl_3$) δ 17.5 (CH_3), 37.6 (CH_2), 102.6 (C-3), 111.3 (C-7), 120.3 (C-5), 120.5 (C-4), 122.4 (C-6), 123.0 (C-6′), 125.8 (C-4′), 127.0 (ArC-H), 128.5 (C-3a), 129.4 (C-2′), 130.8 (ArC-H), 131.8 (C-2), 135.3 (C-1′), 136.9 (C-7a), 168.3 (CO); CI-MS *m/z* 265 $[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{16}N_2O$: 264.1262, found: 264.1260.



The second band (lower R_f) gave 5,14-dihydroindolo[2,1-*d*][1,5]benzodiazocin-6(7*H*)-one **29a** (6.8 mg, 29%) as an off-white solid; mp 269-271 °C (lit.[30] 268-270 °C);); IR (KBr) ν_{max}: 3415 (NH), 1655 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (s, 2H, CH_2-7), 5.18 (s, 2H, CH_2-14), 6.40 (s, 1H, H-8), 7.12 (td, *J*= 7.2, 0.9 Hz, 1H, Ar), 7.24-7.30 (m, 2H, Ar), 7.36-7.41 (m, 1H, Ar), 7.44 (dd, *J*= 7.5, 1.8 Hz, 1H, Ar), 7.48-7.58 (m, 3H, Ar), 7.73 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 35.2 (CH_2-14), 45.5 (CH_2-7), 103.8 (C-8), 108.9, 120.1, 120.7, 121.8, 125.7, 128.1 (C-8a), 128.97, 129.02 (ArC), 130.4, 132.6, 138.3 (ArC), 144.0 (ArC), 170.7 (CO); CI-MS *m/z* 263 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{14}N_2O$: 262.1106, found: 262.1104.

Method B: This method followed the above procedure, apart from the reaction mixture being stirred for 8 min. Solid ammonium chloride was added until the colour dissipated at which point the reaction was allowed to warm to r.t.. The residue was dissolved in ethyl acetate (30 mL), extracted with water (20 mL), dried and concentrated to give a yellow residue. The residue was purified using preparative thin layer chromatography (silica gel, 1% MeOH/DCM) to give the product **29a** (7.8 mg, 35%).

7.2.12 Anionic inducted thermal cyclisation

Attempted cyclisation using $AgBF_4$, $AgPF_6$

To a solution of **161** (20 mg, 0.067 mmol) or **163** (21 mg, 0.066 mmol) in dry CH_3CN (15 mL) was added $AgBF_4$ (3 mg) or $AgPF_6$ (3 mg) and the suspension was heated at reflux under a N_2 atmosphere overnight. The suspension was filtered through silica gel and the solvent was evaporated to dryness to give a purple solid (37 mg). TLC and ^{1}H NMR analysis showed only starting material was obtained.

Attempted cyclisation using $AgBF_4$ in DME

A solution of **178** (90 mg, 0.19 mmol) in dry DME (10 mL) was added $AgBF_4$ (93 mg, 0.48 mmol) and the reaction mixture was stirred at reflux for 4 h under an Ar atmosphere. The DME was evaporated *in vacuo*. The resultant residue was dissolved in EtOAc (50 mL), washed with a 1% aq. TFA solution (3 x 50 mL), then water (3 x 50 mL), dried and concentrated. The resulting oil was subjected to preparative layer chromatography (silica gel, DCM). Only starting material was obtained.

Attempted cyclisation using AgOTf

To a solution of **161** (72 mg, 0.24 mmol) in acetone (2.4 mL) was added NaI (0.37 mmol, 2.48 mmol). The resulting solution was heated at reflux for 2 h. The solution was then cooled to r.t.. EtOAc (15 mL) was added and washed with water (10 mL), dried and concentrated. The residue was immediately dissolved in THF (2.5 mL) and AgOTf (0.11 g, 0.44 mmol) was added. The reaction mixture was allowed to stir for 30 min, then it was poured into EtOAc (20 mL) and washed with satd. $NaHCO_3$ (3 x 15 mL). The organic layer was separated, dried and concentrated to give a yellow residue. ^{1}H NMR spectroscopic analysis showed only starting material was recovered.

Attempted cyclisation using Pd

A mixture of **178** (50 mg, 0.12 mmol), $Pd(Ph_3)_4$ (7 mg, 0.006 mmol), and KOAc (12 mg, 0.12 mmol) in dry DMF (5mL) was heated at reflux under a N_2 atmosphere for 10 h. The reaction mixture was cooled to r.t. and passed through a short column of silica gel. The filtrate was evaporated to dryness. ^{1}H NMR spectroscopic analysis showed only starting material was recovered.

Attempted cyclisation using In powder

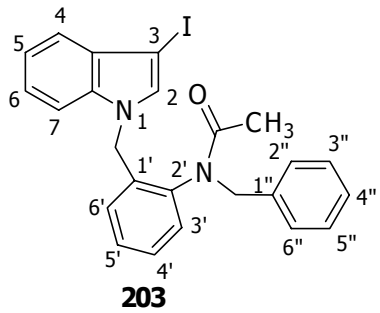
To a solution of **176** (70 mg, 0.16 mmol) in MeOH (0.2 mL) was added water (0.8 mL) dropwise over 5 min at r.t. and then indium powder (60 mg, 0.52 mmol) was added. After being stirred at r.t. for 2 days, the reaction mixture was diluted with water (15 mL) and then extracted with DCM (20 mL). The organic phase was separated, dried and concentrated. The residue was purified using preparative layer chromatography to give 2 major bands. The higher R_f band gave starting material **176** (6 mg, 9%) and the second band gave the simple reduced compound **188c** (1.3 mg, 3%).

Preparation of Zn-Ag couple

Silver acetate (35 mg) in acetic acid (1.25 ml) was heated until boiling. Zinc dust (0.5 g) was then added carefully. A vigorous exothermic reaction followed, stirring was continued for 2 min. and then the mixture was cooled on ice. The suspension was filtered using a sintered funnel and washed with water, methanol and diethyl ether, with filtration between washes. The Zn-Ag couple was dried and stored in a desiccator at r.t..

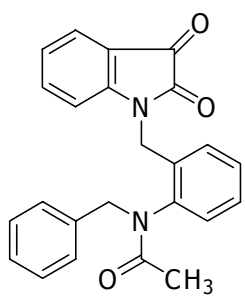
Attempted cyclisation using Zn-Ag couple

A mixture of **178** (0.10 g, 0.21 mmol), Zn-Ag couple (41 mg, 0.63 mmol) in dry THF (15 ml) was heated at 80 ^{o}C in sealed tube under an Ar atmosphere for 5 h with periodic ultrasonication. The reaction mixture was then filtered through celite and washed with cold THF. The filtrate was evaporated, concentrated and the residue subjected to preparative thin layer chromatography (silica gel; 10% EtOAc in pet. spirit) to give two major bands. The higher R_f band gave *N*-benzyl-*N*-{2-[1-(3-iodo-1*H*-indolyl)methyl]phenyl}acetamide **203** (48 mg, 48%) as a yellow solid; mp 153-154 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H, CH_3), 4.69 (d, *J*= 17.1 Hz, 1H, CONC*H*H), 4.69 (d, *J*= 13.8 Hz, 1H, C*H*H), 4.92 (d, *J*= 13.5 Hz, 1H, CH*H*), 5.01 (d, *J*= 16.8 Hz, 1H, CONCH*H*), 6.66 (d, *J*= 7.5 Hz, 1H, H-3′), 6.75 (s, 1H, H-2), 6.94 (m, 1H, H-7), 7.01 (dd, *J*= 7.8, 1.5 Hz, 1H, H-6′), 7.17-7.33 (m, 9H, Ar), 7.44 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 22.5 (CH_3), 46.3 (CON*C*H_2), 52.9 (CH_2), 56.8 (C-3), 109.7 (C-7), 120.9 (C-4), 121.7 (C-6), 123.3 (C-5), 128.3 (C-4′), 128.4 (C-5′), 129.0 (C-2′ and C-6′), 129.3, 129.5, 129.7 (all ArC-H), 130.0 (C-3′ and C-5′), 130.7 (C-3a), 132.1 (C-6′), 135.4 (C-1), 136.7 (C-7a), 137.1 (C-2′), 140.4 (C-1′′), 170.4 (CO); EI-MS *m/z* 480 ([M]$^{+}$, 85%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{24}H_{21}N_2OI$: 480.0699, found: 480.0701.



203

The second band (lower R_f) gave *N*-benzyl-*N*-{2-[(2,3-dioxoindolin-1-yl)methyl]phenyl}acetamide **204** (21 mg, 35%) as a bright yellow solid; mp 75-77 ^{o}C; IR (KBr) ν_{max}: 1743 (C=O), 1651 (C=O) and 1612 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H, CH_3), 4.26 (d, *J*= 16.8 Hz, 1H, C*H*H), 4.83 (d, *J*= 17.1 Hz, 1H, CH*H*), 4.96 (d, *J*= 2.4 Hz, 2H, $CONCH_2$),

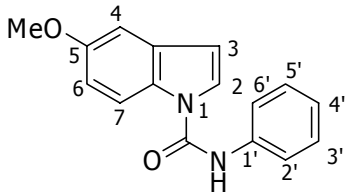


6.15 (d, *J*= 7.8 Hz, 1H, H-7), 7.01 (d, *J*= 6.9, 2.1 Hz, 1H, H-3′), 7.09-7.14 (m , 2H, Ar), 7.29-7.32 (m, 7H, Ar), 7.44 (td, *J*= 8.1, 1.5 Hz, 1H, H-5), 7.63 (dd, *J*= 7.2, 0.9 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 22.7 (CH_3), 40.3 (CH_2), 52.8 (CON*C*H_2), 110.6 (C-7), 117.9 (C-3a), 124.3 (C-5), 125.8 (C-4), 127.1, 128.2 (all ArCH), 128.9 (C-2′′ and C-6′′), 129.2, 129.5 (all ArCH), 129.9 (C-3′′ and C-5′′), 130.1 (C-3′), 132.6 (C-1′), 137.3 (C-2′), 138.6 (C-5), 140.8 (C-1′′), 150.8 (C-7a), 158.4 (C-2), 170.8 (CO), 183.6 (C-3); EI-MS *m/z* 384 ([M]$^+$, 29%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{24}H_{21}N_2O_3$: 385.1552, found: 385.1615.

7.3 Experimental for Chapter 3

7.3.1 *N*-acylation of indoles

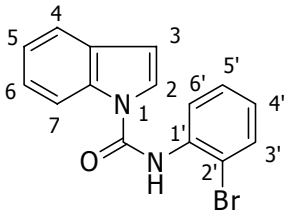
Synthesis of 5-methoxy-*N*-phenyl-1*H*-indole-1-carboxamide (219)



To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 45 mg, 1.12 mmol) in dry DMF (10 mL) at 0-5 ^{o}C was added a solution of 5-methoxyindole (0.15 g, 1.02 mmol) in dry DMF (20 mL) under a N_2 atmosphere and the solution was then stirred at r.t. for 2 h. An excess DMF (20 mL) was added and the mixture was cooled to -60 °C. Phenyl isocyanate (0.11 mL, 1.02 mmol) in DMF (20 mL) was slowly added and the reaction mixture was stirred at r.t. overnight. Solvent was evaporated and DCM (30 mL) was added and then washed with water several times. The DCM phase was dried and concentrated to give a yellow solid. The solid was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **219** (0.33 g, 95%) as white needles; mp 122-123 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 6.59 (d, *J*= 3.0 Hz, 1H, H-3), 6.97 (dd, *J*= 9.3, 2.4 Hz, 1H, H-6), 7.08 (d, *J*= 2.4 Hz, 1H, H-4), 7.18 (dd, *J*= 7.2, 6.9

Hz, 1H, H-4′), 7.32 (br s, 1H, NH), 7.40 (t, *J*= 7.5 Hz, 2H, H-3′ and H-5′), 7.52-7.54 (m, 3H, H-2, H-2′ and H-6′), 8.02 (d, *J*= 8.7 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 55.9 (OCH_3), 103.9 (C-4), 107.9 (C-3), 113.8 (C-6), 115.1 (C-7), 120.6 (C-2′ and C-6′), 124.7 (C-2), 125.0 (C-4′), 129.5 (C-3′ and C-5′), 130.2 (C-3a), 131.4 (C-7a), 137.3 (C-1′), 149.7 (*C*OCH_3), 156.1 (CO); CI-MS *m/z* 267 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{15}N_2O_2$: 267.1134, found: 267.1124.

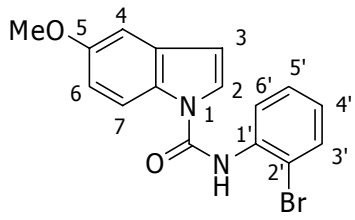
Synthesis of *N*-(2-bromophenyl)-1*H*-indole-1-carboxamide (220a)



To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.12 g, 2.8 mmol) in dry DMF (10 mL) at 0-5 ^{o}C was added a solution of 1*H*-indole (0.30 g, 2.56 mmol) in dry DMF (40 mL) under a N_2 atmosphere and the solution was then stirred at r.t. for 2 h. An excess DMF (20 mL) was added and the mixture was cooled to -60 ^{o}C. 2-Bromophenyl isocyanate (0.40 mL, 3.28 mmol) in DMF (20 mL) was slowly added and the reaction mixture was stirred at r.t. overnight. Solvent was evaporated and DCM (30 mL) was added and then washed with water several times. The DCM phase was dried and concentrated to give a yellow solid. The solid was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **220a** (0.35 g, 43%) as white needles; mp 120-121 ^{o}C; IR (KBr) ν_{max}: 3258 (NH), 1676 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 7.05 (td, *J*= 7.2, 1.5 Hz, 1H, H-4′), 7.29 (dd, *J*= 8.1, 0.9 Hz, 1H, H-4), 7.36 (m, 2H, H-6 and H-5′), 7.60 (m, 3H, H-2, H-5 and H-3′), 8.00 (br s, 1H, NH), 8.25 (d, *J*= 8.1 Hz, 1H, H-7), 8.36 (dd, *J*= 8.7, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 108.6 (C-3), 113.9 (C-2′), 114.5 (C-7), 121.7 (C-6′), 121.8 (ArC-H), 123.1 (C-4), 124.1 (ArC-H), 125.0 (ArC-H), 125.6 (C-4′), 128.9 (ArC-H), 130.7 (C-3a), 132.6 (ArC-H), 135.4 (C-7a), 135.5 (C-1′), 149.2 (CO); CI-MS *m/z* 315 ([M+H; ^{79}Br]$^+$,

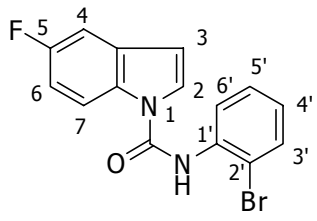
100%), 317 ([M+H; ^{81}Br]$^+$, 99%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{15}H_{12}N_2O^{79}Br$: 315.0133, found: 315.0091.

Synthesis of *N*-(2-bromophenyl)-5-methoxy-1*H*-indole-1-carboxamide (220b)



To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.18 g, 4.49 mmol) in dry DMF (10 mL) at 0-5 ^{o}C was added a solution of 5-methoxy-1*H*-indole (0.60 g, 4.08 mmol) in dry DMF (40 mL) under a N_2 atmosphere and the reaction mixture was then stirred at r.t. for 2 h. An excess DMF (20 mL) was then added and the mixture was cooled to -60 ^{o}C. 2-Bromophenyl isocyanate (0.64 mL, 5.22 mmol) in DMF (20 mL) was slowly added and the reaction mixture was stirred at r.t. overnight. Solvent was evaporated and DCM (30 mL) was added and then washed with water several times. The DCM phase was dried and concentrated to give a yellow solid. The solid was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **220b** (0.80 g, 56%) as white needles; mp 117-118 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 6.67 (dd, *J*= 3.6, 0.9 Hz, 1H, H-3), 7.02 (dd, *J*= 9.0, 2.4 Hz, 1H, H-6), 7.04 (td, *J*= 7.8, 2.4 Hz, 1H, H-4′), 7.10 (d, *J*= 3.0 Hz, 1H, H-4), 7.40 (td, *J*= 8.7, 1.5 Hz, 1H, H-5′), 7.58 (d, *J*= 3.9 Hz, 1H, H-2), 7.60 (dd, *J*= 8.4, 1.2 Hz, 1H, H-3′), 7.95 (br s, 1H, NH), 8.14 (d, *J*= 9.0 Hz, 1H, H-7), 8.35 (dd, *J*= 8.1, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 55.7 (OCH_3), 103.8 (C-4), 108.2 (C-3), 113.6 (C-2′), 113.7 (C-6), 115.1 (C-7), 121.5 (C-6′), 124.3 (C-2), 125.3 (C-4′), 128.7 (C-5′), 130.3 (C-3a), 131.3 (C-7a), 132.4 (C-3′), 135.3 (C-1′), 148.7 (*C*OCH_3), 156.0 (CO); CI-MS *m/z* 345 ([M+H; ^{79}Br]$^+$, 100%), 347 ([M+H; ^{81}Br]$^+$, 99%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{16}H_{14}N_2O_2{}^{81}Br$: 347.0218, found: 347.0204.

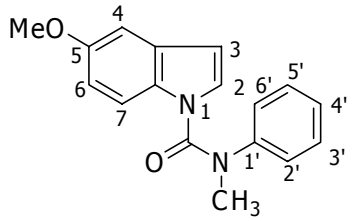
Synthesis of *N*-(2-bromophenyl)-5-fluoro-1*H*-indole-1-carboxamide (220c)



To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.39 g, 8.14 mmol) in dry DMF (10 mL) at 0-5 ^{o}C was added a solution of 5-fluoro-1*H*-indole (1.0 g, 7.40 mmol) in dry DMF (20 mL) under a N_2 atmosphere and the reaction mixture was then stirred at r.t. for 2 h. An excess DMF (20 mL) was added and the mixture was cooled to -60 ^{o}C. 2-Bromophenyl isocyanate (1.20 mL, 9.62 mmol) in DMF (40 mL) was slowly added and the reaction mixture was stirred at r.t. overnight. Solvent was evaporated and DCM (30 mL) was added and then washed with water several times. The DCM phase was dried and concentrated to give a yellow solid. The solid was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **220c** (1.3 g, 53%) as white needles; mp 108-110 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 6.70 (d, *J*= 3.6 Hz, 1H, H-3), 7.06 (t, *J*= 8.4 Hz, 1H, H-4′), 7.14 (td, *J*= 9.0, 2.7 Hz, 1H, H-6), 7.29 (dd, *J*= 9.0, 2.4 Hz, 1H, H-4), 7.41 (t, *J*= 7.8 Hz, 1H, H-5′), 7.63 (m, 2H, H-2 and H-3′), 7.93 (br s, 1H, NH), 8.23 (dd, *J*= 9.0, 4.5 Hz, 1H, H-7), 8.34 (d, *J*= 8.1 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 106.9 (d, *J*= 23.8 Hz, ^{13}C-^{19}F, C4-F), 108.5 (d, *J*= 3.9 Hz, ^{13}C-^{19}F, C3-F), 113.0 (d, *J*= 25.2 Hz, ^{13}C-^{19}F, C6-F), 114.0 (C-2′), 115.8 (d, *J*= 9.2 Hz, ^{13}C-^{19}F, C7-F), 121.8 (C-6′), 125.1 (C-2), 125.7 (C-4′), 128.9 (C-5′), 131.3 (C-3a), 132.1 (C-7a), 132.6 (C-3′), 135.3 (C-1′), 148.9 (CO), 159.5 (d, *J*= 238.0 Hz, ^{13}C-^{19}F, C5-F); CI-MS *m/z* 333 ([M+H; ^{79}Br]$^{+}$, 100%), 335 ([M+H; ^{81}Br]$^{+}$, 95%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{15}H_{11}N_2O_2{}^{81}BrF$: 335.0018, found: 335.0006.

7.3.2 *N*-alkylation procedure

Synthesis of 5-methoxy-*N*-methyl-*N*-phenyl-1*H*-indole-1-carboxamide (221)

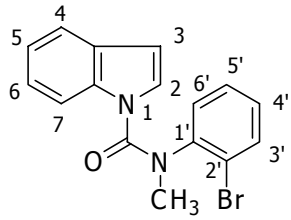


Method A: A suspension of **219** (79 mg, 0.30 mmol) and KOH (66 mg, 1.20 mmol) in dry DMSO (4 mL) was stirred at 0-5 ^{o}C for 30 min. Methyl iodide (38 µL, 0.60 mmol) was then added and the reaction mixture was stirred at r.t. for 16 h. Water (15 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with water (15 mL), dried and evaporated. The residue was subjected to flash column chromatography (silica gel, DCM) to give **221** (36 mg, 43%) as a colourless oil.

Method B: To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 33 mg, 0.83 mmol) in dry THF (10 mL) at 0-5 ^{o}C was added a solution of **219** (0.20 g, 0.75 mmol) in dry THF (40 mL) under a N_2 atmosphere. A solution was stirred at r.t. for 2 h, and a solution of methyl iodide (0.17 mL, 1.88 mmol) in THF (10 mL) was added and then the reaction mixture was stirred at r.t. overnight. THF was evaporated and water (15 mL) was added and the mixture extracted with DCM (3 x 20 mL). The combined DCM extracts were dried and concentrated to give a yellow residue. The residue was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give the title compound **221** (0.16 g, 76%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 6.19 (d, *J*= 3.6 Hz, 1H, H-3), 6.75 (d, *J*= 3.6 Hz, 1H, H-2), 6.93 (dd, *J*= 6.6, 2.4 Hz, 1H, H-6), 6.94 (s, 1H, H-4), 7.05 (dd, *J*= 7.8, 1.2 Hz, 2H, C-3′ and C-5′), 7.16 (t, *J*= 6.9 Hz, 1H, H-4′), 7.27 (t, J= 7.2 Hz, 2H, H-2′ and H-6′), 7.97 (dd, J= 6.9, 2.7 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.8 (CH_3), 55.9 (OCH_3), 103.1 (C-4), 106.1 (C-3), 113.2 (C-6), 115.7 (C-7), 125.1 (C-3′ and C-5′), 126.5 (C-4′), 127.4

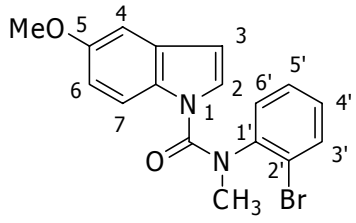
(C-2), 130.0 (C-2′ and C-6′), 130.2 (C-3a), 131.1 (C-7a), 145.0 (C-1′), 154.0 (CO), 155.9 (*C*OCH$_3$); CI-MS *m/z* 281 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{17}H_{17}N_2O_2$: 281.1290, found: 281.1285.

Synthesis of *N*-(2-bromophenyl)-*N*-methyl-1*H*-indole-1-carboxamide (222a)



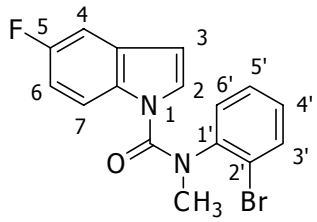
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 13 mg, 0.33 mmol) in dry THF (5 mL) at 0-5 ^{o}C was added a solution of **220a** (94 mg, 0.30 mmol) in THF (20 mL) under a N_2 atmosphere. The solution was stirred at r.t. for 2 h, and a solution of methyl iodide (38 μL, 0.60 mmol) in THF (3 mL) was added and then the reaction mixture was stirred at r.t. overnight. THF was evaporated and water (15 mL) was added and the mixture extracted with DCM (3 x 20 mL). The combined DCM extracts were dried and concentrated to give a yellow residue. The residue was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **222a** (73 mg, 76%) as a white solid; mp 136-137 ^{o}C; IR (KBr) ν_{max}: 1688 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_3), 6.25 (dd, *J*= 3.3, 0.9 Hz, 1H, H-3), 6.79 (d, *J*= 3.9 Hz, 1H, H-2), 7.08-7.13 (m, 2H, H-5 and H-5′), 7.15-7.25 (m, 2H, H-3′ and H-4′), 7.32 (td, *J*= 7.8, 1.2 Hz, 1H, H-6), 7.46 (dd, *J*= 7.8, 0.6 Hz, 1H, H-4), 7.61 (dd, *J*= 7.8, 1.8 Hz, 1H, H-6′), 8.11 (dd, *J*= 7.2, 0.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.0 (CH_3), 106.5 (C-3), 114.9 (C-7), 120.8 (C-4), 122.3 (C-2′), 122.5 (C-5), 124.1 (C-6), 125.9 (C-2), 129.1 (C-3′), 129.3 (C-4′), 129.36 (C-5′), 129.4 (C-3a), 134.4 (C-6′), 136.6 (C-7a), 143.6 (C-1′), 154.1 (CO); CI-MS *m/z* 329 ([M+H; ^{79}Br]$^+$, 100%), 331 ([M+H; ^{81}Br]$^+$, 97%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{16}H_{14}N_2O^{79}Br$: 329.0289, found: 329.0283.

Synthesis of *N*-(2-bromophenyl)-5-methoxy-*N*-methyl-1*H*-indole-1-carboxamide (222b)



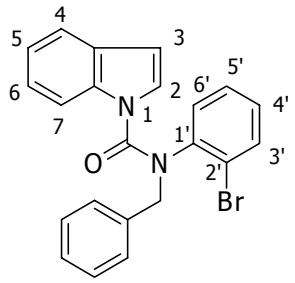
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 34 mg, 0.70 mmol) in dry THF (10 mL) at 0-5 ^{o}C was added a solution of **220b** (0.22 g, 0.64 mmol) in THF (40 mL) under a N_2 atmosphere. The solution was stirred at r.t. for 2 h and a solution of methyl iodide (0.10 mL, 1.60 mmol) in THF (10 mL) was added and then the reaction mixture was stirred at r.t. overnight. THF was evaporated and water (15 mL) was added and the mixture extracted with DCM (3 x 20 mL). The combined DCM extracts were dried and concentrated to give a yellow residue. The residue was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **222b** (0.20, 88%) as a white solid; mp 130-132 ^{o}C; IR (KBr) ν_{max}: 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.18 (dd, *J*= 3.6, 0.6 Hz, 1H, H-3), 6.74 (d, *J*= 3.6 Hz, 1H, H-2), 6.92 (s, 1H, H-4), 6.93 (dd, *J*= 8.4, 2.4 Hz, 1H, H-6), 7.07-7.12 (m, 2H, H-4′ and H-5′), 7.19 (dd, *J*= 6.9, 1.2 Hz, 1H, H-3′), 7.60 (dd, *J*= 7.8, 1.8 Hz, 1H, H-6′), 8.00 (dd, *J*= 8.7, 0.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.0 (CH_3), 55.9 (OCH_3), 103.1 (C-4), 106.4 (C-3), 113.3 (C-6), 115.7 (C-7), 122.3 (C-2′), 126.5 (C-2), 129.1, 129.2 (C-4′ or C-5′), 129.4 (C-3′), 130.1 (C-3a), 131.4 (C-7a), 134.4 (C-6′), 143.7 (C-1′), 154.1 (*C*OCH_3), 155.9 (CO); CI-MS *m/z* 359 ([M+H; ^{79}Br]$^{+}$, 100%), 361 ([M+H; ^{81}Br]$^{+}$, 95%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{17}H_{16}N_2O_2{}^{79}Br$: 359.0395, found: 359.0391.

Synthesis of *N*-(2-bromophenyl)-5-fluoro-*N*-methyl-1*H*-indole-1-carboxamide (222c)



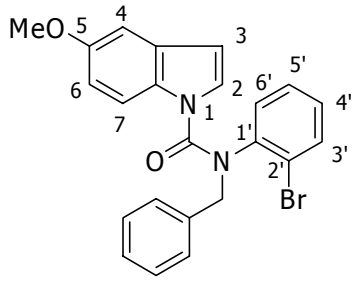
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 40 mg, 0.83 mmol) in dry THF (10 mL) at 0-5 ^{o}C was added a solution of **220c** (0.25 g, 0.75 mmol) in THF (40 mL) under a N_2 atmosphere. The solution was stirred at r.t. for 2 h and a solution of methyl iodide (0.12 mL, 1.88 mmol) in THF (10 mL) was added and the reaction mixture was stirred at r.t. overnight. THF was evaporated and water (15 mL) was added and the mixture extracted with DCM (3 x 20 mL). The combined DCM extracts were dried and concentrated to give a yellow residue. The residue was subjected to flash column chromatography (10% EtOAc/pet. spirit) to give **222c** (0.18 g, 69%) as a white solid; mp 133-134 ^{o}C; IR (KBr) ν_{max}: 1689 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_3), 6.22 (dd, *J*= 3.6, 0.6 Hz, 1H, H-3), 6.83 (d, *J*= 3.3 Hz, 1H, H-2), 7.04 (td, *J*= 9.0, 2.7 Hz, 1H, H-6), 7.09-7.16 (m, 3H, Ar), 7.24 (td, *J*= 6.9, 1.5 Hz, 1H, H-5′), 7.61 (dt, *J*= 7.5, 0.6 Hz, 1H, H-6′), 8.06 (dd, *J*= 8.7, 4.2 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.1 (CH_3), 106.1 (d, *J*= 23.6 Hz, ^{13}C-^{19}F, C6-F), 106.3 (d, *J*= 3.9 Hz, ^{13}C-^{19}F, C3-F), 112.4 (d, *J*= 25.2 Hz, ^{13}C-^{19}F, C4-F), 115.9 (d, *J*= 9.2 Hz, ^{13}C-^{19}F, C7-F), 122.4 (C-2′), 127.5 (C-2), 129.1, 129.4, 129.45 (all ArC-H), 130.1 (d, *J*= 10.3 Hz, ^{13}C-^{19}F, C3a-F), 133.0 (C-7a), 134.5 (C-6′), 143.4 (C-1′), 155.8 (d, *J*= 286.3 Hz, ^{13}C-^{19}F, C5-F), 160.9 (CO); CI-MS *m/z* 347 ([M+H; ^{79}Br]$^{+}$, 100%), 349 ([M+H; ^{81}Br]$^{+}$, 95%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{16}H_{13}N_2O_2{}^{79}BrF$: 347.0195, found: 347.0194.

Synthesis of *N*-benzyl-*N*-(2-bromophenyl)-1*H*-indole-1-carboxamide (223a)



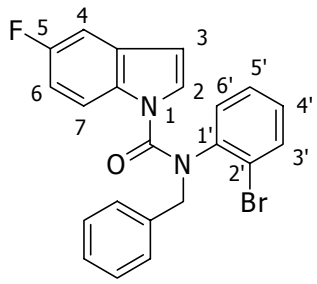
To a suspension of sodium hydride (*ca* 50% dispersion in mineral oil, 88 mg, 1.80 mmol) in dry DMF (10 mL) at 0 ^{o}C was added a solution of **220a** (0.44 g, 1.40 mmol) in DMF (30 mL) followed by addition of *tert*-butylammonium iodide (7 mg). After 30 min, a solution of benzyl bromide (0.26 mL, 2.10 mmol) in DMF (20 mL) was added and the reaction mixture was stirred for 16 h at r.t.. DMF was then evaporated, DCM (20 mL) was added to the residue and the mixture washed with water several times. The DCM phase was dried, concentrated and subjected to flash column chormatography (silica gel, 10% EtOAc/pet. spirit) to give **223a** (0.35 g, 62%) as a white solid; mp 109-111 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 4.63 (br s, 1H, C*H*H), 5.38 (br s, 1H, CH*H*), 6.21 (d, *J*= 3.9 Hz, 1H, H-3), 6.74 (m, 1H, H-3′), 6.80 (d, *J*= 3.6 Hz, 1H, H-2), 7.00-7.04 (m, 2H, H-4′ and H-5′), 7.14 (td, *J*= 7.5, 0.6 Hz, 1H, H-5), 7.20-7.27 (m, 3H, H-6, H-3′′ and H-5′′), 7.30-7.34 (m, 3H, H-2′′, H-4′′ and H-6′′), 7.42 (dd, *J*= 7.5, 0.3 Hz, 1H, H-4), 7.53 (m, 1H, H-6′), 8.11 (d, *J*= 8.4 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 54.3 (CH_2), 106.5 (C-3), 115.1 (C-7), 120.9 (C-4), 122.6 (C-5), 123.0 (C-2′), 124.1 (C-6), 125.9 (C-2), 128.1 (C-4′′), 128.7 (C-3′′ and C-5′′), 128.9, 129.3 (C-4′ and C-5′), 129.4 (C-3a), 129.7 (C-2′′ and C-6′′), 130.7 (C-3′), 134.4 (C-6′), 136.5 (C-7a), 136.8 (C-1′′), 141.4 (C-1′), 153.9 (CO); EI-MS *m/z* 404 ([M; ^{79}Br]$^{+}$, 49%), 406 ([M; ^{81}Br]$^{+}$, 52%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{22}H_{17}N_2OBr$: 404.0524, found: 404.0525.

Synthesis of *N*-benzyl-*N*-(2-bromophenyl)-5-methoxy-1*H*-indole-1-carboxamide (233b)



To a suspension of NaH (*ca* 50% dispersion in mineral oil, 44 mg, 0.91 mmol) in dry DMF (5 mL) at 0 ^{o}C was added a solution of **220b** (0.24 g, 0.70 mmol) in DMF (25 mL) followed by addition of *tert*-butylammonium iodide (3.5 mg). After 30 min, a solution of benzyl bromide (0.13 mL, 1.05 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 h at r.t.. DMF was then evaporated, DCM (20 mL) was added to the residue and the mixture washed with water several times. The DCM phase was dried and concentrated to give a brown oil. The oil was subjected to column chromatography (silica gel, 10% EtOAc/pet. spirit) to give **233b** (0.25 g, 81%) as a white solid; mp 117-118 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H, CH_3), 4.66 (br s, 1H, C*H*H), 5.34 (br s, 1H, CH*H*), 6.08 (dd, *J*= 3.5 Hz, 1H, H-3), 6.69-6.71 (m, 2H, H-2 and Ar), 6.82 (s, 1H, H-4), 6.83 (dd, *J*= 9.0, 2.5 Hz, 1H, H-6), 6.95-6.98 (m, 2H, H-5′ and Ar), 7.17-7.19 (m, 3H, H-3′′, H-5′′ and Ar), 7.24 (dd, *J*= 6.5, 2.5 Hz, 2H, H-2′′ and H-6′′), 7.46 (dd, *J*= 6.5, 2.5 Hz, 1H, H-6′), 7.94 (d, *J*= 9.0 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.0 (CH_2), 55.6 (CH_3), 102.8 (C-4), 106.1 (C-3), 113.0 (C-6), 115.6 (C-7), 122.6 (C-2′), 126.1 (C-2), 127.7 (ArC-H), 128.3 (C-3′′ and C-5′′), 128.4, 128.8, 129.3 (all ArC-H), 129.8 (C-3a), 130.3 (C-2′′ and C-6′′), 131.3 (C-7a), 134.0 (C-6′), 136.2 (C-1′′), 141.3 (C-1′), 153.5 (CO), 155.6 (*C*OCH_3); CI-MS *m/z* 335 ([M+H; ^{79}Br]$^{+}$, 100%), 337 ([M+H; ^{81}Br]$^{+}$, 95%); HRCI-MS *m/z* calcd for $[M+H]^{+}$ $C_{23}H_{20}N_2O_2{}^{81}Br$: 437.0688, found: 437.0669.

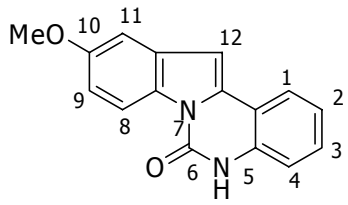
Synthesis of *N*-benzyl-*N*-(2-bromophenyl)-5-fluoro-1*H*-indole-1-carboxamide (223c)



To a suspension of NaH (*ca* 50% dispersion in mineral oil, 44 mg, 0.91 mmol) in dry DMF (5 mL) at 0 ^{o}C was added on a solution of **220c** (0.23 g, 0.70 mmol) in DMF (25 mL), followed by addition of *tert*-butylammonium iodide (3.5 mg). After 30 min, a solution of benzyl bromide (0.13 mL, 1.05 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 h at r.t.. DMF was evaporated, DCM (20 mL) was added to the residue and the mixture washed with water several times. The DCM phase was dried and concentrated to give a brown oil, which was subjected to column chromatography (silica gel, 10% EtOAc/pet. spirit) to give **223c** (0.27 g, 91%) as a white solid; mp 116-118 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 4.64 (br s, 1H, C*H*H), 5.36 (br s, 1H, CH*H*), 6.14 (d, *J*= 3.6 Hz, 1H, H-3), 6.77 (m, 1H, H-3′), 6.80 (d, *J*= 3.6 Hz, 1H, H-2), 6.94-7.06 (m, 4H, Ar), 7.20-7.25 (m, 3H, H-3′′, H-5′′ and Ar), 7.29-7.32 (m, 2H, H-2′′ and H-6′′), 7.50 (m, 1H, H-6′), 8.05 (d, *J*= 9.0, 4.5 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 54.4 (CH_2), 106.11 (d, *J*= 20.0 Hz, ^{13}C-^{19}F, C6-F), 106.3 (C-3), 112.1 (d, *J*= 25.2 Hz, ^{13}C-^{19}F, C4-F), 116.1 (d, *J*= 9.2 Hz, ^{13}C-^{19}F, C7-F), 113.0 (C-2′), 127.4 (C-2), 128.2 (ArC-H), 128.7 (C-3′′ and C-5′′), 129.0 (ArC-H), 129.4 (ArC-H), 129.7 (C-2′′ and C-6′′), 130.1 (d, *J*= 9.8 Hz, ^{13}C-^{19}F, C3a-F), 130.6 (ArC-H), 133.2 (C-7a), 134.4 (C-6′), 136.4 (C-1′′), 154.0 (C-1′), 159.9 (d, *J*= 285.0, ^{13}C-^{19}F, C5-F), 171.8 (CO); CI-MS *m/z* 423 ([M+H; ^{79}Br]$^{+}$, 100%), 425 ([M+H; ^{81}Br]$^{+}$, 95%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{22}H_{16}N_2O^{81}BrF$: 424.0410, found: 424.0415.

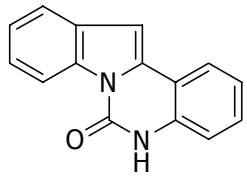
7.3.3 Palladium cyclisation procedure

Attempted synthesis of 10-methoxyindolo[1,2-*c*]quinazolin-6(5*H*)-one (224b)



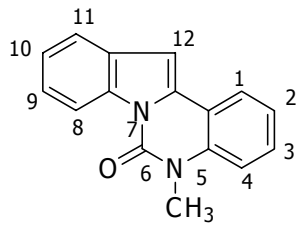
A mixture of **219** (80 mg, 0.30 mmol) and palladium acetate (73 mg, 0.30 mmol) in glacial acetic acid (12 mL) was heated at 110 ^{o}C for 8 h. The reaction mixture was then cooled and the solvent evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using 10% ethyl acetate in pet. spirit as eluant. However, ^{1}H NMR spectroscopic analysis showed that none of the cyclised product was obtained.

Attempted synthesis of indolo[1,2-*c*]quinazolin-6(5*H*)-one (224a)



A mixture of **220a** (94 mg, 0.30 mmol), palladium acetate (7 mg, 0.03 mmol), triphenylphosphine (16 mg, 0.06 mmol), *tert*-butylammonium bromide (98 mg, 0.30 mmol) and K_2CO_3 (84 mg, 0.60 mmol) in dry DMF (25 mL) was heated at 120 ^{o}C under an Ar atmosphere for 3 h. After cooling, the DMF was evaporated and DCM (20 mL) was added and washed with water several times. The DCM layer was washed with brine, dried and evaporated to give a yellow solid. The solid was subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give several fractions, however, ^{1}H NMR spectroscopic analysis showed that none of them contained the title compound.

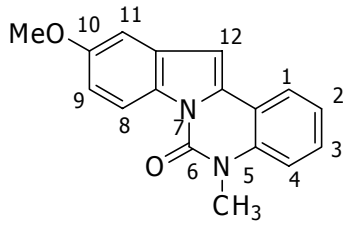
Synthesis of 5-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (225a)



A mixture of **222a** (50 mg, 0.15 mmol), palladium acetate (12 mg, 0.05 mmol), triphenylphosphine (8 mg, 0.03 mmol), *tert*-butylammonium bromide (49 mg, 0.15 mmol) and K_2CO_3 (42

mg, 0.30 mmol) in dry DMF (13 mL) was heated at 120 ^{o}C under an Ar atmosphere for 3 h. After cooling, DMF was evaporated, and then DCM (15 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give compound **225a** (31 mg, 87%) as white needles; mp 181-183 ^{o}C; IR (KBr) ν_{max}: 1677 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, CH_3), 7.03 (d, *J*= 0.6 Hz, 1H, H-12), 7.22 (td, *J*= 8.1, 0.9 Hz, 1H, H-3), 7.24 (td, *J*= 7.5, 0.9 Hz, 1H, H-10), 7.35-7.46 (m, 3H, H-2, H-9, H-10), 7.68 (ddd, *J*= 6.0, 2.1, 0.9 Hz, 1H, H-1), 7.92 (dd, *J*= 8.1, 1.8 Hz, 1H, H-4), 8.69 (ddd, *J*= 5.7, 2.7, 0.9 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 98.3 (C-12), 114.5 (C-8), 115.6 (C-12b), 116.5 (C-11), 120.3 (C-9), 123.3, 123.7, 123.9 (all ArC-H), 124.0 (C-1), 129.4 (C-3), 130.1 (C-12a), 133.3 (C-11a), 134.6 (C-4a), 135.8 (C-7a), 148.2 (CO); CI-MS *m/z* 249 ([M+H]$^{+}$, 100%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{16}H_{13}N_2O$: 249.1028, found: 249.1021.

Synthesis of 10-methoxy-5-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (225b)



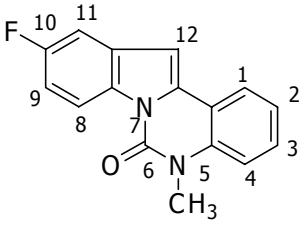
Method A: A mixture of **222b** (37 mg, 0.13 mmol) and palladium acetate (29 mg, 0.13 mmol) in glacial acetic acid (6 mL) was heated at 110 ^{o}C for 48 h. The reaction mixture was then cooled and the solvent evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (silica gel, DCM) to give 2 fractions. The first fraction gave the title compound **225b** (7.3 mg, 20%) as a white solid and the second fraction gave the starting material (3.3 mg, 9%).

Method B: A solution of **222b** (40 mg, 0.18 mmol) and palladium acetate (41 mg, 0.18 mmol) in propanoic acid (6 mL) was heated at reflux at 110 ^{o}C for 48 h. The reaction mixture was then cooled and the solvent evaporated under reduced pressure. The crude reaction residue was purified by column chromatography (silica gel, DCM), however

only starting material (21.5 mg, 33%) could be separated pure. The higher R_f which contained 2 spots could not be separated (preparative thin layer chromatography, 40% DCM/hexane developed 10 times).

Method C: A mixture of **222b** (0.15 g, 0.42 mmol), palladium acetate (40 mg, 0.18 mmol), triphenylphosphine (22 mg, 0.08 mmol), *tert*-butylammonium bromide (0.14 g, 0.42 mmol) and K_2CO_3 (0.12 g, 0.84 mmol) in dry DMF (35mL) was heated at 120 ^oC under an Ar atmosphere for 6 h. After cooling, the DMF was evaporated, and then DCM (15 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give the title compound **225b** (65 mg, 55%); mp 146-147 ^oC; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.99 (s, 1H, H-12), 7.00 (dd, *J*= 9.0, 2.7 Hz, 1H, H-9), 7.12 (d, *J*= 2.7 Hz, 1H, H-11), 7.22-7.28 (m, 2H, H-1 and H-3), 7.44 (td, *J*= 7.5, 1.5 Hz, 1H, H-2), 7.94 (dd, *J*= 7.8, 1.5 Hz, 1H, H-4), 8.57 (d, *J*= 9.3 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 55.8 (OCH_3), 98.1 (C-12), 102.2 (C-8), 113.0 (C-11), 114.5 (C-9), 115.5 (C-12b), 117.3, 123.3, 123.9 (all ArC-H), 129.4 (C-12a), 131.0 (C-11a), 133.9 (C-4a), 135.8 (C-7a), 148.2 (CO), 156.8 (*C*OCH_3); CI-MS *m/z* 279 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{17}H_{15}N_2O_2$: 279.1134, found: 279.1122.

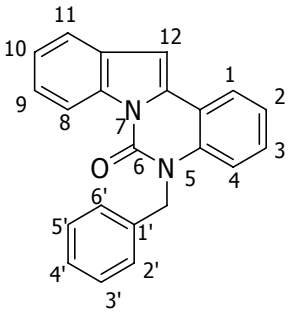
Synthesis of 10-fluoro-5-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (225c)



A mixture of **222c** (0.10 g, 0.29 mmol), palladium acetate (24 mg, 0.10 mmol), triphenylphosphine (16 mg, 0.06 mmol), *tert*-butylammonium bromide (49 mg, 0.15 mmol), and K_2CO_3 (42 mg, 0.30 mmol) in dry DMF (20mL) was heated at 120 ^oC under an Ar atmosphere for 6 h. After cooling, DMF was evaporated, and then DCM (15 mL) was added and washed with water several times. The DCM

layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give the title compound **225c** (59 mg, 76%) as off-white needles; mp 188-189 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3H, CH_3), 6.89 (s, 1H, H-12), 7.05 (td, *J*= 9.0, 2.7 Hz, 1H, H-9), 7.16 (d, *J*= 8.7 Hz, 1H, H-1), 7.19-7.25 (m, 2H, H-2 and H-11), 7.41 (ddd, *J*= 8.1, 7.5, 1.2 Hz, 1H, H-3), 7.84 (dd, *J*= 7.8, 1.2 Hz, 1H, H-4), 8.57 (dd, *J*= 9.0, 5.1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 97.8 (d, *J*= 4.3 Hz, ^{13}C-^{19}F, C12-F), 105.3 (d, *J*= 23.8 Hz, ^{13}C-^{19}F, C11-F), 111.6 (d, *J*= 25.2 Hz, ^{13}C-^{19}F, C9-F), 114.5 (C-4), 115.0 (C-12b), 117.5 (d, *J*= 9.4 Hz, ^{13}C-^{19}F, C8-F), 123.7 (C-2), 124.0 (C-3), 129.7 (C-1), 130.8 (C-11a), 131.0 (C-12a), 134.7 (C-4a), 135.8 (C-7a), 147.8 (CO), 160.0 (d, *J*= 238.5 Hz, ^{13}C-^{19}F, C10-F); CI-MS *m/z* 267 ([M+H]$^{+}$, 100%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{17}H_{12}N_2OF$: 267.0934, found: 267.0926.

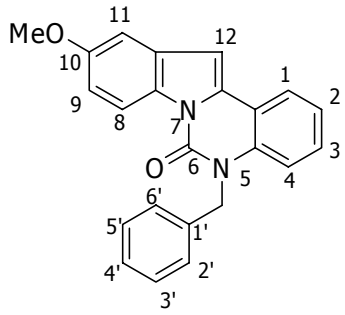
Synthesis of 5-benzylindolo[1,2-*c*]quinazolin-6(5*H*)-one (226a)



A mixture of **223a** (0.30 g, 0.74 mmol), palladium acetate (66 mg, 0.30 mmol), triphenylphosphine (52 mg, 0.20 mmol), *tert*-butylammonium bromide (0.31 g, 0.95 mmol), and K_2CO_3 (0.27 g, 1.92 mmol) in dry DMF (60mL) was heated at 120 ^{o}C under an Ar atmosphere for 6 h. After cooling, DMF was evaporated, and then DCM (25 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAC) to give **226a** (0.16g, 66%) as white needles; mp 141-143 ^{o}C; IR (KBr) ν_{max} 1685 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 2H, CH_2), 7.12-7.16 (m, 2H, H-12 and H-9), 7.22 (td, *J*= 7.5 Hz, 1H, H-10), 7.26-7.34 (m, 6H, Ar), 7.39-7.41 (m, 2H, Ar), 7.72 (dd, *J*= 7.5, 2.1 Hz, 1H, H-11), 7.98 (d, *J*= 7.5 Hz, 1H, H-4), 8.74 (dd, *J*= 8.0, 1.5 Hz, 1H,

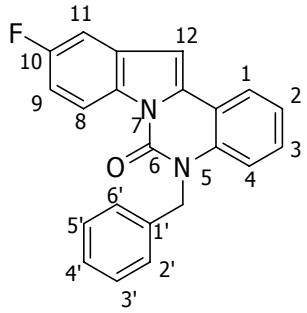
H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.0 (CH_2), 98.6 (C-12), 115.5 (C-9), 115.9 (C-12b), 116.7 (C-8), 120.3 (C-11), 123.5, 123.9, 124.10 (all ArC-H), 124.12 (C-4), 126.7 (C-2′ and C-6′), 127.7 (ArC-H), 129.1 (C-3′ and C-5′), 129.4 (ArC-H), 130.2 (C-11a), 133.4 (C-12a), 134.7 (C-4a), 135.2 (C-7a), 136.5 (C-1′), 148.6 (CO); EI-MS *m/z* 324 ($[M]^+$, 50%); HREI-MS *m/z* calcd for $[M]^+$ $C_{22}H_{16}N_2O$: 324.1263, found: 324.1261.

Synthesis of 5-benzyl-10-methoxyindolo[1,2-*c*]quinazolin-6(5*H*)-one (226b)



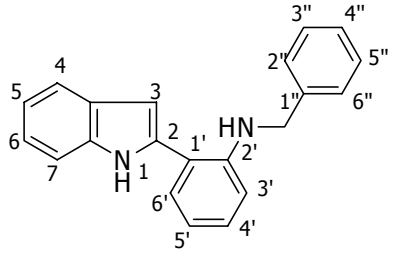
A mixture of **223b** (0.25 g, 0.57 mmol), palladium acetate (52 mg, 0.23 mmol), triphenylphosphine (39 mg, 0.15 mmol), *tert*-butylammonium bromide (0.24 g, 0.73 mmol) and K_2CO_3 (0.20 g, 1.48 mmol) in dry DMF (60mL) was heated at 120 ^oC under an Ar atmosphere for 6 h. After cooling, the DMF was evaporated, and then DCM (25 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give the title compound **226b** (0.18 g, 89%) as white needles; mp 214-215 ^oC; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.02 (dd, *J*= 9.0, 2.7 Hz, 1H, H-9), 7.03 (s, 1H, H-12), 7.14 (s, 1H, H-11), 7.15 (t, *J*= 9.3 Hz, 1H, H-3), 7.02-7.33 (m, 7H, Ar), 7.94 (dd, *J*= 7.8, 1.2 Hz, 1H, H-4), 8.61 (d, *J*= 9.0 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 47.0 (CH_2), 55.9 (CH_3), 98.3 (C-12), 102.3 (C-8), 113.1 (C-11), 115.5 (C-9), 115.7 (C-12b), 117.4, 123.4, 124.0 (all ArC-H), 126.7 (C-2′ and C-6′), 127.7 (ArC-H), 129.1 (C-3′and C-5′), 129.3 (ArC-H), 129.5 (C-11a), 131.2 (C-12a), 134.0 (C-4a), 135.1 (C-7a), 136.5 (C-1′), 148.0 (CO), 157.0 (*C*OCH_3); CI-MS *m/z* 355 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{18}N_2O_2$: 354.1368, found: 354.1386.

Synthesis of 5-benzyl-10-fluoroindolo[1,2-*c*]quinazolin-6(5*H*)-one (226c)



A mixture of **223c** (0.27 g, 0.64 mmol), palladium acetate (58 mg, 0.26 mmol), triphenylphosphine (45 mg, 0.0917 mmol), *tert*-butylammonium bromide (0.26 g, 0.82 mmol) and K_2CO_3 (0.22 g, 1.66 mmol) in dry DMF (60mL) was heated at 120 ^oC under an Ar atmosphere for 6 h. After cooling, the DMF was evaporated, and then DCM (25 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromatography (silica gel, 9:1 pet. spirit/EtOAc) to give the title compound **226c** (0.15 g, 69%) as off-white needles; mp 185-186 ^oC; ^1H NMR ($CDCl_3$) δ 5.45 (s, 2H, CH_2), 6.97 (s, 1H, H-12), 7.03 (td, *J*= 9.0, 2.4 Hz, 1H, H-9), 7.07 (d, *J*= 8.1 Hz, 1H, H-1), 7.15 (t, *J*= 8.1 Hz, 1H, H-3), 7.18-7.28 (m, 7H, Ar), 7.87 (d, *J*= 7.5 Hz, 1H, H-4), 8.59 (dd, *J*= 9.0, 5.1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$), δ 47.1 (CH_2), 98.2 (d, *J*= 4.6 Hz, ^{13}C-^{19}F, C12-F), 105.5 (d, *J*= 23.8 Hz, ^{13}C-^{19}F, C11-F), 111.8 (d, *J*= 25.2 Hz, ^{13}C-^{19}F, C9-F), 115.4 (C-12b), 115.6 (C-4), 117.8 (d, *J*= 9.4 Hz, ^{13}C-^{19}F, C8-F), 123.6 (ArC-H), 124.2 (ArC-H), 126.7 (C-2′ and C-6′), 127.8 (ArC-H), 129.2 (C-3′ and C-5′), 129.8 (ArC-H), 131.1 (C-11a), 131.2 (C-12a), 134.9 (C-4a), 135.2 (C-7a), 136.3 (C-1′), 148.4 (CO), 160.2 (d, *J*= 238.5 Hz, ^{13}C-^{19}F, C10-F); CI-MS *m/z* 343 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{22}H_{16}N_2OF$: 343.1247, found: 343.1249.

Synthesis of 2-(*N*-benzylaminophenyl)-1*H*-indole (227a)

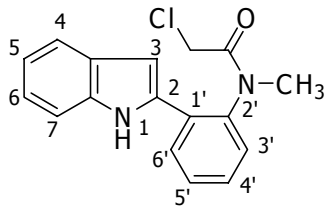


Method A: A stirred suspension of **212a** (0.57g, 2.74 mmol) and K_2CO_3 (0.38 g, 2.74 mmol) in dry THF (25 ml) was cooled to 0-5 ^oC and a solution of benzyl bromide (0.36 mL, 3.01 mmol) in THF (5 mL) was added dropwise. Stirring was continued with cooling and the reaction mixture was then

stirred at r.t. overnight. Water (30 mL) was added to the reaction and the mixture extracted with DCM (3 x 20 mL). The organic layers were combined, dried and evaporated to yield a yellow solid. The solid was subjected to flash column chromatography (silica gel, 1:1 hexane/DCM) to give **227a** (0.37 g, 45%) as a yellow solid (however the colour turned to blue after contact with air); ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 2H, CH_2), 5.03 (br s, 1H, NH), 6.65-6.68 (m, 2H, H-3 and H-3′), 6.75 (t, *J*= 7.2 Hz, 1H, H-5′), 7.06-7.31 (m, 10H, Ar), 7.58 (d, *J*= 7.8 Hz, 1H, H-4), 8.17 (br s, 1H, indole NH); ^{13}C NMR ($CDCl_3$) δ 48.6 (CH_2), 102.0 (C-3), 111.1 (C-7), 111.9 (C-3′), 117.7 (C-5′), 118.9 (C-1′), 120.4 (C-4), 120.7 (C-6), 122.4 (C-5), 127.4 (C-2′′ and C-6′′), 127.5 (C-4′′), 129.0 (C-3′′ and C-5′′), 129.2 (C-3a), 129.6 (C-6′), 129.7 (C-4′), 135.8 (C-2), 136.4 (C-7a), 139.4 (C-1′′), 145.9 (C-2′); CI-MS *m/z* 299 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{21}H_{19}N_2$: 299.1548, found: 299.1543.

7.3.4 Hydrolysis and chloroacetylation

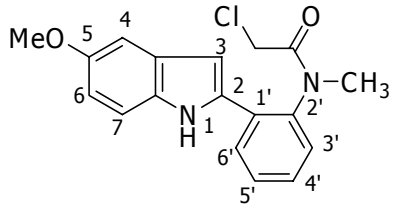
Synthesis of *N*-[2-(1*H*-indol-2-yl)phenyl]-*N*-methylchloroacetamide (228a)



Compound **225a** (26 mg, 0.10 mmol) was heated at reflux in 25% NaOH (6 mL) and EtOH (10 mL) for 24 h. The EtOH was evaporated and water (15 mL) was added and extracted with DCM (3x 15 mL). The organic layer was separated, dried and concentrated to give a blue solid. The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (50 mg, 0.43 mmol) and dry THF (10 mL) were added. The reaction mixture was stirred at 0-5 ^{o}C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (23 μL, 0.30 mmol) in THF (3 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (15 mL)

was then added. The reaction mixture was washed with water (3 x 10 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give the title compound **228a** (21 mg, 70%) as a yellow solid; mp 84-86 ^{o}C; IR (KBr) ν_{max}: 3310 (NH), 1655 (C=O), 747 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.16 (s, 3H, CH_3), 3.81 (d, *J*= 12.6 Hz, 1H, C*H*HCl), 3.87 (d, *J*= 14.1 Hz, 1H, CH*H*Cl), 6.56 (s, 1H, H-3), 7.08 (t, *J*= 7.8 Hz, 1H, H-5), 7.18-7.59 (m, 2H, Ar), 7.30-7.39 (m, 2H, Ar), 7.45 (t, *J*= 7.8 Hz, 1H, H-5′), 7.58 (d, *J*= 7.8 Hz, 1H, H-4), 7.69 (d, *J*= 8.1 Hz, 1H, H-6′), 8.37 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 37.2 (CH_3), 41.9 (CH_2Cl), 103.6 (C-3), 111.3 (C-7), 120.8 (C-5), 121.3 (C-4), 123.5 (C-6), 129.0 (C-3a), 129.35, 129.4, 129.65, 129.7 (all ArC-H), 132.0 (C-1′), 133.5 (C-2), 135.0 (C-7a), 140.0 (C-2′), 167.3 (CO); CI-MS *m/z* 299 ([M+H]$^{+}$, 100%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{17}H_{16}N_2O^{35}Cl$: 299.0951, found: 299.0945.

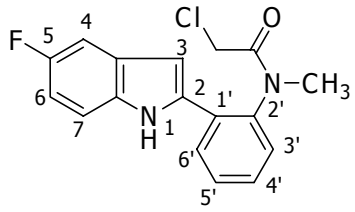
Synthesis of *N*-[2-(5-methoxy-1*H*-indol-2-yl)phenyl]-*N*-methylchloroacetamide (228b)



Compound **225b** (35 mg, 0.14 mmol) was heated at reflux in 25% NaOH (10 mL) and EtOH (25 mL) for 48 h. The EtOH was then evaporated and water (20 mL) was added and extracted with DCM (3x 20 mL). The organic layer was separated, dried, and concentrated to give a blue solid. The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.10 g, 0.74 mmol) and dry THF (10 mL) were added. The reaction mixture was stirred at 0-5 ^{o}C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (42 μL, 0.53 mmol) in THF (3 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 15 mL) and the DCM layer was separated, dried and

concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give the title compound **228b** (29 mg, 64%) as a yellow solid; mp 88-89 ^{o}C; IR (KBr) ν_{max}: 3314 (NH), 1653 (C=O), 763 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.23 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 3.89 (d, *J*= 5.1 Hz, 2H, CH_2Cl), 6.40 (d, *J*= 1.2 Hz, 1H, H-3), 6.90 (dd, *J*= 8.7, 2.4 Hz, 1H, H-6), 7.08 (d, *J*= 2.1 Hz, 1H, H-4), 7.30 (d, *J*= 8.7 Hz, 2H, H-7 and H-3′), 7.41 (td, *J*= 8.1, 0.9 Hz, 1H, H-4′), 7.49 (t, *J*= 7.8 Hz, 1H, H-5′), 7.73 (d, *J*= 7.8 Hz, 1H, H-6′), 8.32 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ 37.3 (CH_3), 41.9 (CH_2Cl), 55.8 (OCH_3), 102.2 (C-3), 103.2 (C-4), 112.3 (C-6), 113.9 (C-7), 128.4 (C-3′), 129.1 (C-3a), 129.4, 129.7, 129.8 (all ArC-H), 130.7 (C-1′), 132.0 (C-2), 135.0 (C-7a), 139.0 (C-2′), 155.0 (*C*OCH_3), 167.0 (CO); CI-MS *m/z* 329 ([M+H; ^{35}Cl]$^{+}$, 32%); HRCI-MS *m/z* calcd for $[M+H]^{+}$ $C_{18}H_{18}N_2O_2{}^{37}Cl$: 331.1027, found: 331.1032.

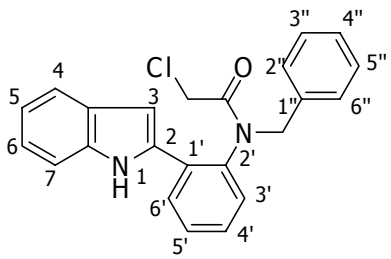
Synthesis of *N*-[2-(5-fluoro-1*H*-indol-2-yl)phenyl]-*N*-methylchloroacetamide (228c)



Compound **225c** (50 mg, 0.19 mmol) was heated at reflux in 25% NaOH (10 mL) and EtOH (25 mL) for 24 h. The EtOH was then evaporated and water (20 mL) was added and extracted with DCM (3 x 20 mL). The organic layer was separated, dried and concentrated to give a blue solid. The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.10 g, 0.74 mmol) and dry THF (10 mL) were added. The reaction mixture was stirred at 0-5 ^{o}C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (42 μL, 0.53 mmol) in THF (5 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 15 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give the title compound **228c** (46 mg, 79%) as a yellow solid; mp 175-176 ^{o}C; IR (KBr) ν_{max}: 3315 (NH), 1654 (C=O), 764 (C-Cl) cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 3.21 (s, 3H, NCH_3), 3.84 (d, *J*= 12.9 Hz, 1H, C*H*HCl), 3.91 (d, *J*= 12.9 Hz, 1H, CH*H*Cl), 6.64 (d, *J*= 2.1 Hz, 1H, H-3), 6.95 (td, *J*= 9.3, 2.4 Hz, 1H, H-6), 7.23-7.35 (m, 4H, Ar), 7.40-7.51 (m, 2H, Ar), 7.76 (dd, *J*= 7.5, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 37.3 (CH_3), 41.9 (CH_2Cl), 103.3 (d, *J*= 4.6 Hz, ^{13}C-^{19}F, C3-F), 105.9 (d, *J*= 23.5 Hz, ^{13}C-^{19}F, C4-F), 111.9 (d, *J*= 26.3 Hz, ^{13}C-^{19}F, C6-F), 112.2 (d, *J*= 9.5 Hz, ^{13}C-^{19}F, C7-F), 129.2 (d, *J*= 10.4 Hz, ^{13}C-^{19}F, C3a-F), 129.5 (C-6′), 129.6, 129.7, 129.8 (all ArC-H), 130.2 (C-1′), 133.7 (C-2), 135.0 (C-7a), 139.2 (C-2′), 158.4 (d, *J*= 234.2 Hz, ^{13}C-^{19}F, C5-F), 167.2 (CO); CI-MS *m/z* 317 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{14}N_2O^{35}ClF$: 316.0779, found: 316.0778.

Synthesis of *N*-benzyl-*N*-[2-(1*H*-indol-2-yl)phenyl]chloroacetamide (229a)

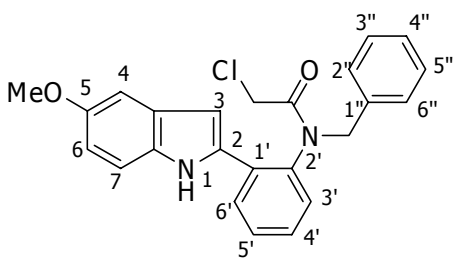


Method A; A suspension of **227a** (0.20 g, 0.67 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) in dry THF (25 mL) was cooled to 0-5 ^oC and a solution of chloroacetyl chloride (0.13 mL, 1.68 mmol) in THF (10 mL) was then added dropwise and the reaction mixture stirred at r.t. overnight. The solvent was then evaporated under reduced pressure. Water (15 mL) was added and the mixture extracted with DCM (2 x 15 mL). The combined organic extracts were dried and concentrated to give a yellow residue. The residue was subjected to flash column chromatography (silica gel, 1: 1 hexane/DCM) to give the chloroacetamide **229a** (0.20 g, 79%) as a yellow solid.

Method B; Compound **225a** (0.14g, 0.10 mmol) was heated at reflux in 25% NaOH (27 mL) and EtOH (40 mL) for 24 h. The EtOH was then evaporated and water (40 mL) was added and extracted with DCM (3 x 30 mL). The organic layer was separated, dried and concentrated to give a blue solid. The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.23 g, 1.7 mmol) and dry THF (20 mL) were added. The

reaction mixture was stirred at 0-5 ^{o}C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (96 μL, 1.20 mmol) in THF (10 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 25 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give the title compound **229a** (0.20g, 79%) as a yellow solid; mp 139-141 ^{o}C; IR (KBr) ν_{max}: 3311 (NH), 1638 (C=O), 745 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.74 (d, *J*= 13.5 Hz, 1H, C*H*HCl), 3.87 (d, *J*= 13.2 Hz, 1H, C*H*HCl), 4.58 (d, *J*= 14.1 Hz, 1H, C*H*H), 5.17 (d, *J*= 13.8 Hz, 1H, CH*H*), 6.69 (d, *J*= 2.4 Hz, 1H, H-3), 7.03 (dd, *J*= 8.1, 1.2 Hz, 1H, H-3′), 7.12 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.25 (m, 2H, Ar), 7.31 (m, 3H, Ar), 7.46 (td, *J*= 7.8, 1.5 Hz, 1H, H-5′), 7.61 (dd, *J*= 7.5, 0.9 Hz, 1H, H-4), 7.71 (dd, *J*= 7.8, 1.2 Hz, 1H, H-6′), 7.86 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2Cl), 53.7 (CH_2), 103.6 (C-3), 111.4 (C-7), 120.6 (C-4), 121.1 (C-6), 123.3 (C-5), 128.5 (C-3′), 128.6 (C-3a), 129.0 (C-2′′ and C-6′′), 129.1 (ArC-H), 129.6 (C-3′′ and C-5′′), 129.9 (ArC-H), 130.1 (ArC-H), 131.0 (C-1′), 133.6 (C-2), 136.2 (C-7a), 136.8 (C-2′), 137.2 (C-1′′), 166.8 (CO); CI-MS *m/z* 375 ([M+H]$^{+}$, 11%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{23}H_{20}N_2O^{35}Cl$: 375.1264; found: 375.1267.

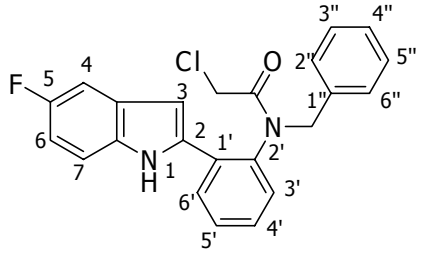
Synthesis of *N*-benzyl-*N*-[2-(5-methoxy-1*H*-indol-2-yl)phenyl]chloroacetamide (229b)



Compound **226b** (0.12 g, 0.22 mmol) was heated at reflux in 25% NaOH (30 mL) and EtOH (40 mL) for 48 h. The EtOH was then evaporated and water (20 mL) was added and extracted with DCM (3 x 20 mL). The organic layer was separated, dried and concentrated to give a blue solid. The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.11 g,

0.79 mmol) and dry THF (15 mL) were added. The reaction mixture was stirred at 0-5 ^{o}C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (71 μL, 0.55 mmol) in THF (5 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 15 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give the title compound **229b** (97 mg, 71%) as a yellow solid; mp 109-111 ^{o}C; IR (KBr) ν_{max}: 3297 (NH), 1655 (C=O), 736 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.75 (d, *J*= 13.5 Hz, 1H, C*H*HCl), 3.84 (s, 3H, CH_3), 3.88 (d, *J*= 13.8 Hz, 1H, CH*H*Cl), 4.44 (d, *J*= 13.8 Hz, 1H, C*H*H), 5.26 (d, *J*= 14.1 Hz, 1H, CH*H*), 6.61 (dd, *J*= 2.1, 0.9 Hz, 1H, H-3), 6.85 (dd, *J*= 9.0, 2.4 Hz, 1H, H-6), 6.97 (dd, *J*= 8.1, 1.5 Hz, 1H, H-3′), 7.06 (d, *J*= 2.4 Hz, 1H, H-4), 7.13 (d, *J*= 8.7 Hz, 1H, H-7), 7.21-7.32 (m, 6H, Ar), 7.42 (td, *J*= 7.5, 1.2 Hz, 1H, H-5′), 7.73 (dd, *J*= 7.8, 1.3 Hz, 1H, H-6′), 8.17 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.5 (CH_2Cl), 53.4 (CH_2), 56.0 (OCH_3), 102.2 (C-3), 103.2 (C-4), 112.3 (C-6), 114.0 (C-7), 128.5 (ArC-H), 128.9 (ArC-H), 129.0 (C-2′′ and C-6′′), 129.2 (C-3a), 129.6 (ArC-H), 129.8 (ArC-H), 129.9 (C-3′′ and C-5′′), 130.7 (C-6′), 130.9 (C-1′), 132.2 (C-2), 134.1 (C-7a), 136.3 (C-2′), 137.0 (C-1′′), 154.7 (*C*OCH_3), 167.0 (CO); CI-MS *m/z* 405 ([M+H; ^{35}Cl]$^{+}$, 100%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{24}H_{21}N_2O_2{}^{37}Cl$: 406.1262; found: 406.1208.

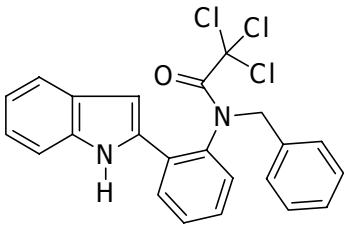
Synthesis of *N*-benzyl-*N*-[2-(5-fluoro-1*H*-indol-2-yl)phenyl]chloroacetamide (229c)



Compound **226c** (0.13 g, 0.38 mmol) was heated at reflux in 25% NaOH (30 mL) and EtOH (40 mL) for 24 h. The EtOH was then evaporated and water (20 mL) was added and extracted with DCM (3 x 20 mL). The organic layer was separated, dried and concentrated to give a blue solid. The

solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.19 g, 1.37 mmol) and dry THF (30 mL) were added. The reaction mixture was stirred at 0-5 ^oC under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (76 μL, 0.53 mmol) in THF (15 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 15 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to preparative layer chromatography (silica gel, 10% EtOAc/pet. spirit) to give the title compound **229c** (90 mg, 82%) as a yellow solid; mp 202-203 ^oC; ^1H NMR ($CDCl_3$) δ 3.70 (d, *J*= 13.2 Hz, 1H, C*H*HCl), 3.82 (d, *J*= 13.2 Hz, 1H, CH*H*Cl), 4.64 (d, *J*= 14.1 Hz, 1H, C*H*H), 5.07 (d, *J*= 13.8 Hz, 1H, CH*H*), 6.60 (d, *J*= 1.8 Hz, 1H, H-3), 6.91 (td, *J*= 9.0, 2.4 Hz, 1H, H-6), 7.04-7.08 (m, 2H, H-4 and Ar), 7.19-7.31 (m, 6H, Ar), 7.34 (td, *J*= 7.8, 1.8 Hz, 1H, H-4′), 7.44 (td, *J*= 7.2, 0.9 Hz, 1H, H-5′), 7.68 (dd, J= 7.8, 1.5 Hz, 1H, H-6′), 7.77 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.3 (CH_2Cl), 53.8 (CH_2), 103.6 (d, *J*= 4.8 Hz, ^{13}C-^{19}F, C3-F), 105.7 (d, *J*= 23.5 Hz, ^{13}C-^{19}F, C4-F), 111.8 (d, *J*= 26.3 Hz, ^{13}C-^{19}F, C6-F), 112.2 (d, *J*= 9.8 Hz, ^{13}C-^{19}F, C7-F), 128.7 (ArC-H), 129.2 (C-2′′ and C-6′′), 129.5 (ArC-H), 129.7 (ArC-H), 130.1 (C-3′′ and C-5′′), 130.1 (ArC-H), 130.6 (ArC-H), 130.8 (C-1′), 133.4 (C-2), 135.4 (C-7a), 136.1 (C-2′), 137.3 (C-1′′), 159.2 (d, *J*= 240.0 Hz, ^{13}C-^{19}F, C5-F), 166.9 (CO); CI-MS *m/z* 393 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{18}N_2OClF$: 392.1092, found: 392.1091.

Synthesis of *N*-benzyl-*N*-[2-(1*H*-indol-2-yl)phenyl]trichloroacetamide (230)

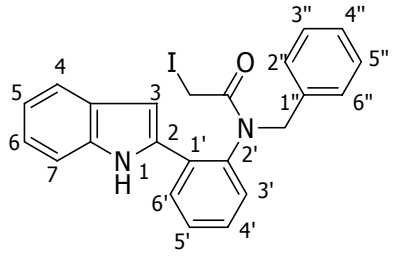


Compound **226a** (0.14 g, 0.47 mmol) was heated at reflux in 25% NaOH (30 mL) and EtOH (40 mL) for 24 h. The EtOH was then evaporated and water (20 mL) was added

and extracted with DCM (3 x 20 mL). The organic layer was separated, dried and concentrated to give a blue solid (^{1}H NMR spectroscopic analysis showed that no starting material remained). The solid was dried on a high vacuum pump for 2-3 h and then K_2CO_3 (0.23 g, 1.70 mmol) and dry THF (45 mL) were added. The reaction mixture was stirred at 0-5 ^oC under a N_2 atmosphere for 30 min and a solution of trichloroacetyl chloride (0.13 mL, 1.20 mmol) in THF (20 mL) was then added and the mixture stirred overnight at r.t.. The THF was evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3 x 15 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to PTLC (silica gel, 10% EtOAc/pet. spirit) to give, in the first fraction, compound **226a** (26 mg, 17%), and in the second fraction, the title compound **230** (44 mg, 21%) as a yellow solid; mp 99-101 ^oC; ^{1}H HMR (acetone-d_6) δ 3.95 (br s, 1H, C*H*H), 5.70 (br s, 1H, CH*H*), 7.05-7.10 (m, 2H, H-3 and H-5′), 7.15-7.26 (m, 9H, Ar), 7.47-7.50 (m, 2H, H-4 and Ar), 7.66 (d, *J*= 8.1 Hz, 1H, H-6′), 7.91 (br s, 1H, NH); ^{13}C NMR (Acetone-d_6) δ 56.6 (CH_2), 103.0 (CCl_3), 111.6 (C-4), 120.1 (C-3), 120.9 (C-6′), 122.8 (C-4′), 127.4, 128.1, 128.5, 129.3 (all ArC-H), 130.9 (C-3a), 132.1 (C-5′), 134.9 (C-1′), 137.0 (C-2′), 137.4 (C-2), 145.9 (C-7a), 148.1 (C-1′′), 160.9 (CO); ES-MS *m/z* 442 ($[M]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{17}N_2OCl_3$: 442.0406, found: 442.0405.

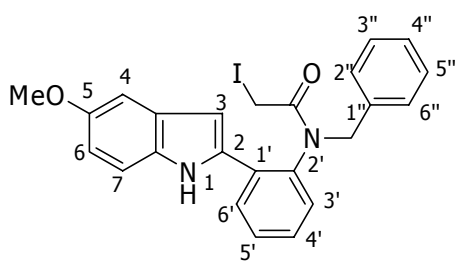
7.3.5 Preparation of iodoacetamides

Synthesis of *N*-benzyl-*N*-[2-(1*H*-indol-2-yl)phenyl]iodoacetamide (231a)



To a solution of chloroacetamide **229a** (0.20 g, 0.53 mmol) in acetonitrile (20 mL) was added NaI (0.78 g, 5.30 mmol), and the mixture was stirred at r.t. for 15 h. The solvent was evaporated to dryness *in vacuo*. The residue was dissolved in DCM (25 mL), and the mixture was washed with water (3 x 15 mL), dried and concentrated. The solid obtained was chromatographed through a short column (silica gel, DCM) to give **231a** (0.23 g, 92%) as a yellow solid; mp 168-169 ^{o}C; IR (KBr) ν_{max}: 3312 (NH), 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.59 (d, *J*= 10.2 Hz, 1H, C*H*HI), 4.54 (d, *J*= 13.8 Hz, 1H, C*H*H), 5.17 (d, *J*= 13.8 Hz, 1H, CH*H*), 6.69 (dd, *J*= 2.1, 0.6 Hz, 1H, H-3), 7.12 (m, 2H, Ar), 7.20 (m, 2H, Ar), 7.25 (m, 2H, Ar), 7.32 (m, 4H, Ar), 7.44 (td, *J*= 8.7, 1.2 Hz, 1H, H-5′), 7.61 (d, *J*= 7.8 Hz, 1H, H-4), 7.70 (dd, *J*= 7.8, 1.2 Hz, 1H, H-6′), 7.94 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ -1.9 (CH_2I), 53.3 (CH_2), 103.3 (C-3), 111.1 (C-7), 120.3 (C-4), 120.8 (C-6), 122.9 (C-5), 128.2 (C-3′), 128.4 (C-3a), 128.7 (ArC-H), 128.8 (C-2′′ and C-6′′), 129.2 (ArC-H), 129.6 (C-3′′ and C-5′′), 129.7 (ArC-H), 130.1 (ArC-H), 130.5 (C-1′), 133.4 (C-2), 136.2 (C-7a), 136.6 (C-2′), 137.8 (C-1′′), 168.1 (CO); CI-MS *m/z* 467 ([M+H]$^{+}$, 15%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{23}H_{20}N_2OI$: 467.0620, found 467.0612.

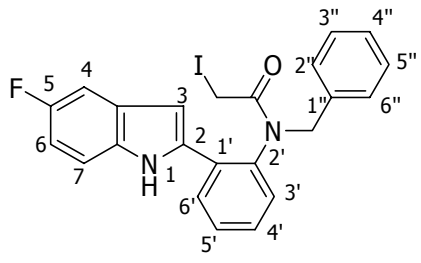
Synthesis of *N*-benzyl-*N*-[2-(5-methoxy-1*H*-indol-2-yl)phenyl]iodoacetamide (231b)



To a solution of chloroacetamide **229b** (97 mg, 0.24 mmol) in acetonitrile (20 mL) was added NaI (0.36 g, 2.40 mmol), and the mixture was stirred at

r.t. for 16 h. The solvent was evaporated to dryness *in vacuo*. The residue was dissolved in DCM (15 mL), and the mixture was washed with water (3 x 10 mL), dried and concentrated. The solid obtained was passed through a short column chromatography (silica gel, DCM) to give **231b** (65 mg, 55%) as a yellow solid; mp 138-139 ^{o}C; IR (KBr) ν_{max}: 3311 (NH), 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (d, *J*= 9.9 Hz, 1H, C*H*HI), 3.56 (d, *J*= 10.2 Hz, 1H, CH*H*I), 3.84 (s, 3H, OCH_3), 4.44 (d, *J*= 13.8 Hz, 1H, C*H*H), 5.24 (d, *J*= 13.8 Hz, 1H, CH*H*), 6.62 (d, *J*= 2.4 Hz, 1H, H-3), 6.84 (dd, *J*= 9.0, 2.4 Hz, 1H, H-6), 7.03-7.13 (m, 3H, Ar), 7.24-7.32 (m, 6H, Ar), 7.42 (t, *J*= 7.5 Hz, 1H, H-5′), 7.71 (dd, *J*= 7.8, 1.5 Hz, 1H, H-6′), 8.05 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ -1.5 (CH_2I), 53.5 (CH_2), 56.0 (OCH_3), 102.3 (C-3), 103.3 (C-4), 112.3 (C-6), 113.9 (C-7), 128.4 (ArC-H), 128.8 (ArC-H), 129.0 (C-2′′ and C-6′′), 129.2 (C-3a), 129.5 (ArC-H), 129.7 (ArC-H), 129.8 (C-3′′ and C-5′′), 130.4 (ArC-H), 130.8 (C-1′), 132.2 (C-2), 134.3 (C-7a), 136.5 (C-2′), 138.0 (C-1′′), 154.7 (*C*OCH_3), 168.5 (CO); CI-MS *m/z* 497 ([M+H]$^{+}$, 14%); HREI-MS *m/z* calcd for [M]$^{+}$ $C_{24}H_{21}N_2O_2I$: 496.0648; found: 496.0643.

Synthesis of *N*-benzyl-*N*-[2-(5-fluoro-1*H*-indol-2-yl)phenyl]iodoacetamide (231c)

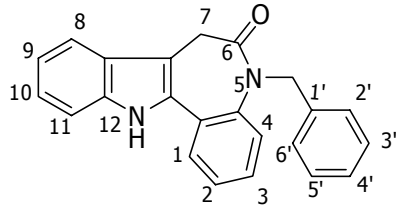


To a solution of chloroacetamide **229c** (90 mg, 0.31 mmol) in acetonitrile (10 mL) was added NaI (0.46 g, 3.10 mmol), and the mixture was stirred at r.t. for 16 h. The solvent was evaporated to dryness *in vacuo*. The residue was dissolved in DCM (15 mL) and washed with water (3 x 10 mL). The organic extract was dried, concentrated and chromatographed through a short column (silica gel, DCM) to give the title compound **231c** (0.10 g, 68%) as a yellow solid; mp 172-173 °C; IR (KBr) ν_{max}: 3297 (NH), 1636 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (d, *J*= 10.2 Hz, 1H, C*H*HI), 3.53 (d, *J*= 10.2 Hz, 1H, CH*H*I), 4.62 (d, *J*= 14.1 Hz, 1H,

C*H*H), 5.11 (d, *J*= 14.1 Hz, 1H, CH*H*), 6.63 (d, *J*= 2.1 Hz, 1H, H-3), 6.92 (td, *J*= 9.3, 2.7 Hz, 1H, H-6), 7.09 (dd, *J*= 8.7, 4.5 Hz, 1H, H-7), 7.16 (dd, *J*= 7.8, 1.2 Hz, 1H, H-3′), 7.21-7.33 (m, 6H, Ar), 7.36 (td, *J*= 7.5, 1.5 Hz, 1H, H-4′), 7.46 (td, *J*= 7.8, 1.5 Hz, 1H, H-5′), 7.70 (dd, *J*= 7.8, 1.5 Hz, 1H, H-6′), 7.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ -1.8 (CH_2I), 53.8 (CH_2), 103.6 (d, *J*= 5.2 Hz, ^{13}C-^{19}F, C3-F), 105.7 (d, *J*= 23.5 Hz, ^{13}C-^{19}F, C4-F), 111.7 (d, *J*= 26.6 Hz, ^{13}C-^{19}F, C6-F), 112.1 (d, *J*= 9.7 Hz, ^{13}C-^{19}F, C7-F), 128.6 (ArC-H), 129.0 (d, *J*= 10.5 Hz, ^{13}C-^{19}F, C3a-F), 129.1 (C-2′′ and C-6′′), 129.4 (ArC-H), 129.5 (ArC-H), 129.6 (C-3′′ and C-5′′), 130.2 (ArC-H), 130.3 (ArC-H), 130.6 (C-1′), 133.4 (C-2), 135.5 (C-7a), 136.3 (C-2′), 138.1 (C-1′′), 158.4 (d, *J*= 221.1 Hz, ^{13}C-^{19}F, C5-F), 168.4 (CO); CI-MS *m/z* 485 ($[M+H]^+$, 25%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{18}N_2OFI$: 484.0448, found: 484.0497.

7.3.6 Radical cyclisation

Cyclisation of 231a in toluene

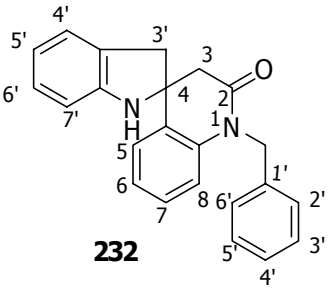


To a boiling solution of **231a** (60 mg, 0.13 mmol) in toluene (9 mL) under a N_2 atmosphere was added dropwise a solution of tri-*n*-butyltin hydride (70 μL, 0.26 mmol) and AIBN (21 mg, 0.13 mmol) in toluene (33 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (20 mL) and satd. KF (20 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for 2 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 70:30) to give compound **96a** (11 mg, 25%) as yellow needles, mp 214-216 ^{o}C; IR (KBr) ν_{max}: 3270 (NH), 1646 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-

d_6) δ 3.37 (d, *J*= 13.5 Hz, 1H, C*H*H-7), 3.73 (d, *J*= 14.0 Hz, 1H, C*H*H-7), 4.88 (d, *J*= 16.0 Hz, 1H, C*H*H), 5.08 (d, *J*= 16.0 Hz, 1H, CH*H*), 6.76 (d, *J*= 7.0 Hz, 2H, H-2′ and H-6′), 7.00 (m, 3H, H-3′, H-4′ and H-5′), 7.11 (t, *J*= 8.0 Hz, 1H, H-9), 7.16 (t, *J*= 7.5 Hz, 1H, H-10), 7.21 (td, *J*= 8.0, 1.5 Hz, 1H, H-2), 7.27 (t, *J*= 7.5 Hz, 1H, H-3), 7.47 (m, 2H, H-4 and H-11), 7.72 (d, *J*= 7.5 Hz, 1H, H-8), 7.75 (dd, *J*= 8.0, 1.5 Hz, 1H, H-1), 11.62 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 35.3 (CH_2-7), 53.2 (CH_2), 110.1 (C-7a), 112.7 (C-11), 118.7 (C-8), 121.2 (C-10), 122.5 (C-9), 125.0 (C-4), 125.3 (C-7b), 126.7 (C-2), 126.8 (C-2′ and C-6′), 127.5 (C-3), 128.2 (C-1), 128.9 (C-3′ and C-5′), 130.2 (C-12b), 133.4 (C-12a), 137.0 (C-11a), 138.2 (C-4a), 138.5 (C-1′), 169.4 (CO); CI-MS m/z 339 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{23}H_{19}N_2O$: 339.1497, found: 339.1498.

Cyclisation of 231a in de-gassed toluene

To a boiling solution of **231a** (70 mg, 0.15 mmol) in boiling de-gassed toluene (11 mL) under an Ar atmosphere was added dropwise a solution of tri-*n*-butyltin hydride (80 μL, 0.30 mmol) and AIBN (24 mg, 0.15 mmol) in de-gassed toluene (38 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (30 mL) and satd. KF (30 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for 2 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 70:30).



232

The first fraction gave spiro[(1,2,3,4 tetrahydroquinolin-2-one)-4,2′-(2,3-dihydro-1*H*-indole)] **232** (6.4 mg, 13%) and the second fraction gave **96a** (4 mg, 8%).

232 was obtained as a yellow solid; mp 61-62 ^{o}C; IR

(KBr) ν_{max}: 3350 (NH), 1654 (C=O) cm^{-1}; ^{1}H ($CDCl_3$) δ 2.89 (d, *J*= 15.3 Hz, 1H, C*H*H-7), 3.03 (d, *J*= 15.9 Hz, 1H, C*H*H-3′), 3.09 (d, *J*= 15.6 Hz, 1H, CH*H*-3), 3.31 (d, *J*= 15.6 Hz, 1H, CH*H*-3′), 3.95 (br s, 1H, NH), 5.13 (d, *J*= 16.2 Hz, 1H, C*H*H), 5.33 (d, *J*= 16.2 Hz, 1H, CH*H*), 6.70 (d, *J*= 8.1 Hz, 1H, H-7′), 6.74 (t, *J*= 7.2 Hz, 1H, H-5′), 6.95 (d, *J*= 8.1 Hz, 1H, H-8), 7.00 (t, *J*= 7.8 Hz, 1H, H-6), 7.04-7.11 (m, 2H, H-4′ and H-6′), 7.16 (td, *J*= 7.5, 1.2 Hz, 1H, H-7), 7.22-7.26 (m, 3H, H-2′, H-4′ and H-6′), 7.30-7.36 (m, 2H, H-3′ and H-5′), 7.54 (dd, *J*= 7.5, 0.1 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2-3), 44.8 (CH_2), 46.3 (CH_2-3′), 63.7 (C-4), 109.3 (C-7′), 116.3 (C-5′), 119.5 (C-8), 123.9 (C-6), 124.7 (C-7), 125.5 (C-5), 126.1 (C-3′a), 126.8 (C-2′ and C-6′), 127.5, 128.1, 128.8 (all ArC-H), 129.0 (C-3′ and C-5′), 133.5 (C-4a), 137.0 (C-8a), 138.2 (C-1′), 149.4 (C-7a), 168.9 (CO); EI-MS *m/z* 340 ($[M]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{23}H_{21}N_2O$: 341.1654, found: 341.1638.

Cyclisation of 231a in toluene on a larger scale

To a boiling solution of **231a** (0.17 g, 0.36 mmol) in toluene (25 mL) under a N_2 atmosphere was added dropwise a solution of tri-*n*-butyltin hydride (0.20 mL, 0.73 mmol) and AIBN (59 mg, 0.36 mmol) in toluene (92 mL) over 4 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (50 mL) and satd. KF (50 mL) were added to the residue and the mixture was stirred vigorously at r.t. for 6 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 70:30) to give the spiro **232** (12 mg, 10%) and some unidentified compounds.

Cyclization of 231a in mesitylene

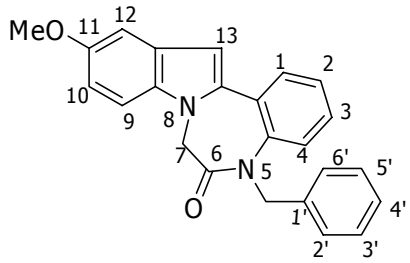
To a boiling solution of **231a** (60 mg, 0.13 mmol) in mesitylene (9 mL) was added dropwise a solution of tri-*n*-butyltin hydride (70 μL, 0.26 mmol) and AIBN (21

mg, 0.13 mmol) in mesitylene (30 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (30 mL) and satd. KF (30 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for 2 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 70:30) to give compound **96a** (23 mg, 52%).

Cyclisation of 231b

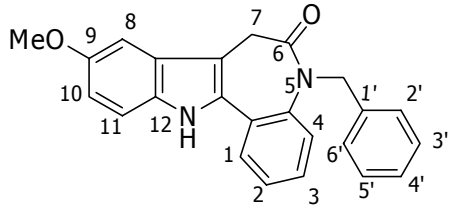
To a boiling solution of **231b** (55 mg, 0.11 mmol) in mesitylene (20 mL) was added dropwise a solution of tri-*n*-butyltin hydride (59 μL, 0.22 mmol) and AIBN (18 mg, 0.11 mmol) in mesitylene (60 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (30 mL) and satd. KF (30 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for 2 h. The organic extract was separated, dried, and concentrated. The residue was chromatographed on silica gel (AcOEt/pet. spirit, 9:1).

The first fraction gave 5-benzyl-11-methoxy-5*H*-indolo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one **233** (12 mg, 30%) as a yellow solid; mp 153-154 ^{o}C; IR (KBr) ν_{max}: 1670 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.56 (d, *J*= 13.0 Hz, 1H, C*H*H), 4.97 (d, *J*= 15.0 Hz, 1H, CH*H*), 5.01 (d, *J*= 16.0 Hz, 1H, C*H*H-7), 5.10 (d, *J*= 14.5 Hz, 1H, CH*H*-7), 6.69 (s, 1H, H-13), 6.95 (dd, *J*= 9.0, 2.5 Hz, 1H, H-10), 7.00 (d, *J*= 7.5 Hz, 1H, H-4), 7.14 (d, *J*= 2.5 Hz, 1H, H-12), 7.16-7.20 (m, 3H, H-3, H-2′ and H-6′), 7.27 (td, *J*= 8.5, 1.5 Hz, 1H, H-2), 7.31-7.34 (m, 3H, H-3′, H-4′ and H-5′), 7.43 (d, *J*= 8.5 Hz, 1H, H-9), 7.65 (dd, *J*= 7.5, 1.5 Hz, 1H, H-1), ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.7 (CH_2), 52.6 (CH_2-7), 55.9 (OCH_3), 99.5 (C-13), 102.3 (C-12), 110.0 (C-9), 112.8 (C-10), 123.4 (C-4′), 126.4 (C-



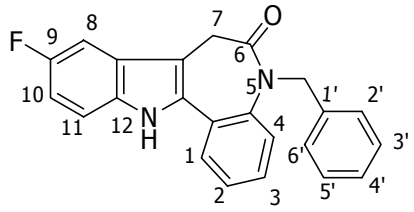
2), 126.8 (C-2′ and C-6′), 127.1 (C-4), 127.2 (C-13b), 128.5 (C-3′ and C-5′), 128.7 (C-13a), 129.0 (C-3), 130.4 (C-1), 131.7 (C-12a), 136.8 (C-1′), 137.5 (C-8a), 139.2 (C-4a), 154.6 ($COCH_3$), 167.2 (CO); EI-MS *m/z* 368 ($[H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{20}N_2O_2$: 368.1525, found: 368.1529.

The second fraction gave 5-benzyl-7,12-dihydro-9-methoxy-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one **96b** (10 mg, 25%) as an off-white solid; mp 213-215 ^oC; IR



(KBr) ν_{max}: 3300 (NH), 1647 (C=O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.54 (br s, 2H, CH_2-7), 3.08 (s, 3H, CH_3), 5.08 (br s, 2H, CH_2), 6.83 (dd, *J*= 8.5, 2.5 Hz, 1H, H-10), 6.90 (d, *J*= 6.5 Hz, 2H, H-2′ and H-6′), 7.10-7.15 (m, 3H, H-3′, H-4′ and H-5′), 7.21 (d, *J*= 2.5 Hz, 1H, H-8), 7.29 (t, *J*= 7.0 Hz, 1H, H-2), 7.32-7.36 (m, 2H, H-11 and H-3), 7.55 (d, *J*= 8.5 Hz, 1H, H-4), 7.65 (dd, *J*= 7.5, 1.5 Hz, 1H, H-1), 11.57 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.7 (CH_2-7), 52.1 (CH_2), 55.4 (OCH_3), 99.7 (C-8), 109.7 (C-7a), 112.4 (C-11), 112.8 (C-10), 124.2 (C-4), 125.1 (C-2), 126.3 (C-2′ and C-6′), 126.3 (C-7b), 126.4 (C-12b), 126.6 (C-4′), 127.2 (C-1), 127.8 (C-3), 128.2 (C-3′ and C-5′), 132.6 (C-11a), 133.0 (C-12a), 137.9 (C-1′), 138.9 (C-4a), 153.6 (*C*OCH_3), 170.3 (CO); CI-MS m/z 369 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{20}N_2O_2$: 368.1525, found: 368.1531.

5-benzyl-9-fluoro-7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one (96c)



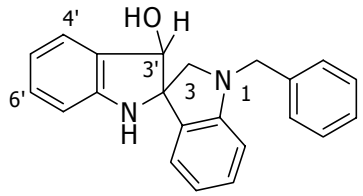
To a boiling solution of **231c** (50 mg, 0.10 mmol) in mesitylene (20 mL) was added dropwise a solution of tri-*n*-butyltin hydride (54 μL, 0.20 mmol) and AIBN (16 mg, 0.10 mmol) in mesitylene (60 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (30 mL) and satd. KF (30 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for

2 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (AcOEt/pet. spirit, 9:1) to give off white needles of **96c** (16 mg, 45%); mp 247-248 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.50 (d, *J*= 13.5 Hz, 1H, C*H*H-7), 3.91 (d, *J*= 13.8 Hz, 1H, CH*H*-7), 5.05 (d, *J*= 15.6 Hz, 1H, C*H*H), 5.14 (d, *J*= 15.4 Hz, 1H, CH*H*), 6.95 (td, *J*= 8.7, 2.4 Hz, 1H, H-10), 7.03-7.05 (m, 2H, H-2′ and H-6′), 7.15-7.17 (m, 2H, H-3′ and H-5′), 7.23-7.27 (m, 2H, H-11 and Ar), 7.30-7.39 (m, 2H, H-2 and Ar), 7.43-7.51 (m, 2H, H-8 and Ar), 7.83 (d, *J*= 7.2 Hz, 1H, H-1), 10.09 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 35.6 (CH_2-7), 54.6 (CH_2), 103.9 (d, *J*= 24.1 Hz, ^{13}C-^{19}F, C8-F), 110.5 (d, *J*= 25.8 Hz, ^{13}C-^{19}F, C10-F), 111.1 (C-7a), 112.7 (d, *J*= 9.8 Hz, ^{13}C-^{19}F, C11-F), 124.4 (ArC-H), 125.7 (d, *J*= 10.0 Hz, ^{13}C-^{19}F, C7b-F), 126.4 (ArC-H), 126.5 (ArC-H), 126.8 (C-2′ and C-6′), 127.2 (C-4′), 128.0 (C-1), 128.7 (C-3′ and C-5′), 129.1 (C-12b), 129.8 (C-12a), 133.2 (C-11a), 137.6 (C-1′), 138.8 (C-4a), 159.0 (d, *J*= 230.6 Hz, ^{13}C-^{19}F, C9-F), 169.4 (CO); CI-MS m/z 357 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{17}N_2OF$: 356.1325, found: 356.1381.

Cyclisation of trichloroacetamide 230

To a boiling solution of trichloroacetamide **230** (40 mg, 0.09 mmol) in mesitylene (20 mL) was added dropwise a solution of tri-*n*-butyltin hydride (48 μL, 0.18 mmol) and AIBN (14 mg, 0.09 mmol) in mesitylene (60 mL) over 2 h, and the reaction mixture was heated at reflux for 16 h. After evaporating the solvent, diethyl ether (30 mL) and satd. KF (30 mL) were added to the residue, and the mixture was stirred vigorously at r.t. for 2 h. The organic extract was separated, dried and concentrated. The residue was chromatographed on silica gel (AcOEt/pet. spirit, 9:1) to give two major fractions.

The first fraction gave spiro[(1-benzyl-2,3-dihydro-1*H*-indole)-3,2′-(3′-hydroxy-2′,3′-dihydro-1*H*-indole)] **235** (3.1 mg, 11%) and the second fraction gave **226a** (3.2 mg, 11%).

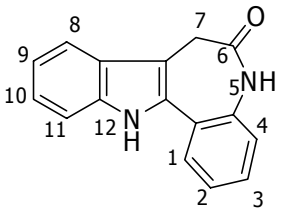


235

235 obtained as a yellow solid; mp 137-138 ^{o}C; ^{1}H NMR (500 MHz, CD_3CN) δ 3.60 (d, *J*= 16.5 Hz, 1H, C*H*H-2), 3.93 (d, *J*= 16.5 Hz, 1H, CH*H*-2), 4.18 (br s, 1H, OH), 5.01 (br d, *J*= 17.0 Hz, 2H, C*H*H and NH), 5.52 (d, *J*= 16.5 Hz, 1H, CH*H*), 6.48 (s, 1H, H-3′), 6.83 (d, *J*= 8.0 Hz, 1H, H-7), 7.05-7.10 (m, 2H, H-5′ and H-6′), 7.17-7.20 (m, 2H, H-5 and H-6), 7.25-7.28 (m, 4H, H-4, H-2′, H-4′ and H-6′), 7.43 (d, *J*= 7.5 Hz, 3H, H-4, H-3′ and H-5′), 8.45 (d, *J*= 8.5 Hz, 1H, H-7′); ^{13}C NMR (125 MHz, CD_3CN) δ 32.9 (CH_2-2), 41.2 (CH_2), 65.9 (C-2′), 71.6 (C-3′), 108.6 (C-7), 109.6 (C-7), 115.9 (C-3a), 116.2, 117.1, 118.3 (all ArCH), 120.9 (C-3′ and C-5′), 121.1 (ArCH), 121.9 (C-4), 122.0 (C-3a), 122.3 (C-4′), 122.7 (C-2′ and C-6′), 123.8 (ArCH), 131.7 (C-1′), 132.5 (C-7a), 137.5 (C-7′a); CI-MS m/z 329 ([M+H]$^{+}$, 15%); HRCI-MS *m/z* calcd for [M+H]$^{+}$ $C_{22}H_{21}N_2O$: 329.1654, found: 329.1643.

7.3.7 Debenzylation

7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one (96)



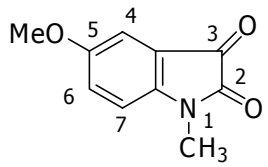
Sodium metal (*ca* 30 mg) was added to dry THF (2 mL) under a N_2 atmosphere and then the mixture was frozen using a liquid N_2 bath. Liquid ammonia (condensed at –70 ^{o}C, *ca* 7 mL) and a solution of **96a** (26 mg, 0.08 mmol) in dry THF (2 mL) were added. The frozen mixture was warmed to –60 ^{o}C and the mixture was stirred for at r.t. for 10 min. Solid ammonium chloride was then added until the colour dissipated at which point the reaction was allowed to warm to r.t.. The residue was

dissolved in ethyl acetate (30 mL), extracted with water (3 x 20 mL), dried and concentrated to give a yellow residue. The residue was purified using PTLC (silica gel, 1% MeOH/DCM) to give the title compound **96** (8 mg, 40%) as a yellow solid; mp >272 ^{o}C (lit.[77] >315 ^{o}C); ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 2H, CH_2), 7.11 (ddd, *J*= 7.2, 6.9, 1.5 Hz, 1H, H-9), 7.16 (ddd, *J*= 7.5, 6.9, 1.5 Hz, 1H, H-10), 7.23-7.29 (m, 3H, H-2, H-3 and H-4), 7.44 (dd, *J*= 7.2, 1.5 Hz, 1H, H-11), 7.80 (d, *J*= 6.9 Hz, 1H, H-8), 7.85 (m, 1H, H-1), 10.08 (s, 1H, NH), 11.62 (br s, 1H, indole NH); ^{13}C NMR ($CDCl_3$) δ 35.7 (CH_2), 109.7 (C-7a), 112.5 (C-11), 118.7 (C-8), 120.7 (C-9), 122.1 (C-10), 123.3 (ArC-H), 124.8 (ArC-H), 125.9 (C-12b), 126.3 (ArC-H), 126.9 (C-7b), 128.2 (C-1), 132.2 (C-12a), 134.8 (C-4a), 136.9 (C-11a), 170.3 (CO); EI-MS *m/z* 248 ([M]+, 100%), HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{13}N_2O$: 249.1028, found: 249.1032.

7.4 Experimental for Chapter 4

7.4.1 Synthesis of *N*-substituted 5-methoxyindole-2,3-dione

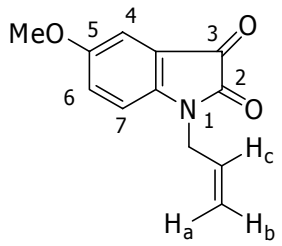
Synthesis of 5-methoxy-1-methylindole-2,3-dione (243a)



A suspension of 5-methoxyindole-2,3-dione (0.50 g, 2.82 mmol) and anhydrous K_2CO_3 (0.56 g, 4.05 mmol) in dry DMF (30 mL) was stirred at 0-5 ^{o}C for 30 min. Methyl iodide (0.19 mL, 3.10 mmol) was then added and the reaction mixture was heated at 80 ^{o}C for 10 h. DMF was evaporated and DCM (30 mL) was added and then washed with water (25 mL) several times. The organic extract was separated, dried and evaporated to give a red residue. The residue was subjected to flash column chromatography (silica gel, DCM) to give the 5-methoxy-1-methylindole-2,3-dione **243a** (0.36 g, 67%) as red crystals; mp 170-172 ^{o}C (lit.[206] 173-174 °C); ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3),

6.80 (d, *J*= 7.8, 0.9 Hz, 1H, H-7), 7.12-7.16 (m, 2H, H-4 and H-6); ^{13}C NMR ($CDCl_3$) δ 26.5 (CH_3), 56.2 (OCH_3), 109.8 (C-4), 111.1 (C-6), 118.0 (C-3a), 124.8 (C-7), 145.6 (C-7a), 156.9 (*C*OCH_3), 158.5 (C-2), 184.0 (C-3); EI-MS *m/z* 191 ($[M]^+$, 100%); HREI-MS *m/z* calc. for $[M]^+$ $C_{10}H_9NO_3$: 191.0582, found: 191.0583.

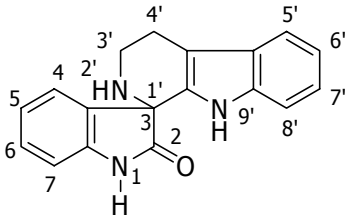
Synthesis of 1-allyl-5-methoxyindole-2,3-dione (243b)



A suspension of 5-methoxyindole-2,3-dione (0.52 g, 2.94 mmol) and anhydrous K_2CO_3 (0.56 g, 4.05 mmol) in dry DMF (30 mL) was stirred at 0-5 ^{o}C for 30 min. Allyl bromide (0.27 mL, 3.12 mmol) was then added and the reaction mixture was heated at 80 ^{o}C for 10 h. DMF was evaporated and DCM (30 mL) was added and washed with water (25 mL) several times. The organic extract was separated, dried and evaporated to give a red residue. The residue was subjected to flash column chromatography (silica gel, DCM) to give the 1-allyl-5-methoxyindole-2,3-dione **243b** (0.63 g, 99%) as red crystals; mp 81-82 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 4.34 (d, *J*= 5.5 Hz, 2H, CH_2), 5.29 (d, *J*= 11.5 Hz, 1H, CH_aH_b), 5.32 (d, *J*= 11.0 Hz, 1H, CH_aH_b), 5.84 (m, 1H, CH_c), 6.82 (d, *J*= 8.0 Hz, 1H, H-7), 7.12 (dd, *J*= 8.0, 2.5 Hz, 1H, H-6), 7.15 (d, *J*= 2.5 Hz, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.7 (CH_2), 56.2 (CH_3), 109.7 (C-4), 112.2 (CH_aH_b), 118.2 (C-3a), 118.8 (C-6), 124.9 (C-7), 130.8 (CH_c), 145.0 (C-7a), 156.7 (C-5), 158.2 (C-2), 183.8 (C-3); EI-MS *m/z* 217 ($[M]^+$, 47%); HREI-MS *m/z* calcd for $[M]^+$ $C_{12}H_{11}NO_3$: 217.0739, found: 217.0739.

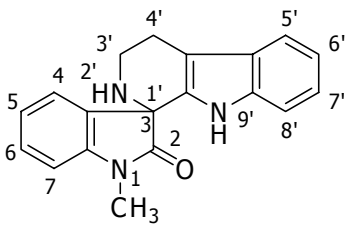
7.4.2 Condensation between isatins and tryptamine

Preparation of spiro[(3*H*-indol-2-one)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (250a)



A mixture of isatin (0.74 g, 5.0 mmol) and tryptamine (0.80 g, 5.0 mmol) in EtOH (25 mL) in the presence of glacial acetic acid (0.10 mL) was stirred at r.t. for 24 h. The solid formed was suction filtered, washed with cold water and air dried to give the title compound **250a** (1.3 g, 89%) as a yellow solid; mp 157-158 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 2.00 (br s, 1H, NH-2′), 2.88 (s, 2H, CH_2-4′), 3.23 (m, 1H, C*H*H-3′), 3.58 (m, 1H, CH*H*-3′), 6.58 (d, *J*= 7.5 Hz, 1H, H-7), 6.90-6.94 (m, 2H, H-5 and H-8′), 6.99-7.10 (m, 4H, H-4, H-6, H-6′ and H-7′), 7.51 (d, *J*= 7.2 Hz, 1H, H-5′), 8.21 (br s, 1H, NH-9′), 9.04 (br s, 1H, NH-1); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_2-4′), 40.1 (CH_2-3′), 62.3 (C-1′), 111.1 (C-7), 111.4 (C-8′), 112.3 (C-4a′), 118.6 (C-5′), 119.6 (C-6′), 122.6 (C-7′), 123.3 (C-5), 125.0 (C-4), 127.2 (C-9a′), 129.9 (C-6), 130.0 (C-4b′), 132.3 (C-3a), 136.5 (C-8a′), 141.0 (C-7a), 179.6 (CO); CI-MS *m/z* 290 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd. for $[M]^+$ $C_{18}H_{15}N_3O$: 289.1215, found: 289.1217.

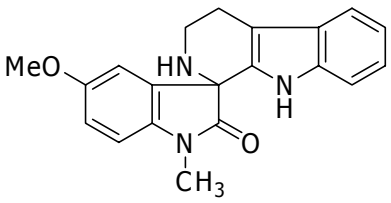
Preparation of spiro[(*N*-methyl-3*H*-indol-2-one)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (250b)



A mixture of 1-methylisatin (0.16 g, 0.93 mmol) and tryptamine (0.16 g, 1.00 mmol) in EtOH (5 mL) in the presence of glacial acetic acid (0.02 mL) was stirred at r.t. for 24 h. The solid formed was suction filtered, washed with cold water and air dried to give the title compound **250b** (0.15 g, 54%) as a yellow solid; mp 239-241 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 2.04 (br s, 1H, NH-2′), 2.93 (t, *J*= 5.4 Hz,

2H, CH_2-4′), 3.20 (s, 3H, CH_3), 3.30 (m, 1H, C*H*H-3′), 3.79 (m, 1H, CH*H*-3′), 6.84-6.89 (m, 2H, H-7 and H-8′), 7.01 (t, *J*= 7.5 Hz, 1H, H-5), 6.07-7.17 (m, 3H, H-4, H-5′ and H-7′), 7.32 (t, *J*= 7.8 Hz, 1H, H-6′), 7.55 (t, *J*= 7.5 Hz, 1H, H-6), 7.76 (br s, 1H, NH); ^{13}C NHR ($CDCl_3$) δ 22.3 (CH_2-4′), 26.8 (CH_3), 40.2 (CH_2-3′), 61.7 (C-1′), 109.0 (C-7), 110.2 (C-8′), 111.3 (C-5′), 112.6 (C-4a′), 118.7 (C-6′), 119.7 (C-7′), 123.5 (C-5), 124.9 (C-4), 127.3 (C-9a′), 130.1 (C-6), 131.7 (C-4b′), 136.4 (C-8a′), 138.7 (C-3a), 143.8 (C-7a), 176.9 (CO); EI-MS *m/z* 303 ([M]$^+$, 28%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{19}H_{18}N_3O$: 304.1450, found: 304.1456.

Preparation of spiro[(5-methoxy-*N*-methyl-3*H*-indol-2-one)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (250c)



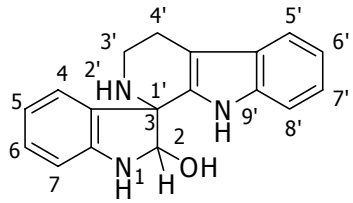
A mixture of **243a** (0.36 g, 1.88 mmol) and tryptamine (0.30 g, 1.88 mmol) in EtOH (25 mL) in the presence of glacial acetic acid (0.10 mL) was stirred at r.t. for 24 h. The solid formed was suction filtered, washed with cold water and air dried to give the title compound **250c** (0.35 g, 56%) as a yellow solid; mp 255-256 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 2.76 (m, 2H, CH_2-4′), 3.14 (s, 3H, CH_3), 3.16 (m, 1H, C*H*H-3′), 3.32 (br s, 1H, NH), 3.60 (m, 1H, CH*H*-3′), 3.65 (s, 3H, OCH_3), 6.75 (d, *J*= 2.1 Hz, 1H, H-4), 6.94 (td, *J*= 8.4, 2.4 Hz, 1H, H-6), 6.96-7.04 (m, 3H, Ar), 7.15 (d, *J*= 8.1 Hz, 1H, H-8′), 7.45 (d, *J*= 7.5 Hz, 1H, H-5′), 10.37 (br s, 1H, indole NH); ^{13}C NMR (DMSO-d_6) δ 22.6 (C-4′), 26.9 (CH_3), 39.6 (C-3′), 56.2 (OCH_3), 61.9 (C-1′), 109.9 (C-7), 111.0 (C-4a′), 111.8 (C-8′), 111.9 (C-4), 114.5 (C-6), 118.5 (C-5′), 119.1 (C-6′), 121.9 (C-7′), 127.2 (C-4b′), 132.2 (C-9a′), 133.8 (C-8a′), 136.7 (C-7a), 137.9 (C-3a), 156.2 ($COCH_3$), 176.8 (CO); EI-MS *m/z* 333 ([M]$^+$, 69%); HREI-MS m/z calcd. for [M]$^+$ $C_{20}H_{19}N_3O_2$: 333.1477, found: 333.1472.

Attempted preparation of spiro[(*N*-allyl-5-methoxy-3*H*-indol-2-one)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (250d)

A mixture of **243b** (0.43 g, 1.98 mmol) and tryptamine (0.34 g, 2.12 mmol) in EtOH (25 mL) in the presence of glacial acetic acid (0.10 mL) was stirred at r.t. for 48 h. The solid formed was suction filtered, washed with cold water and air dried to give a red solid. The solid was subjected to flash column chromatography (silica gel, 9:1 pet. spirit/hexane) to give three fractions. However, ^{1}H NMR spectroscopic analysis of the fractions were still mixtures.

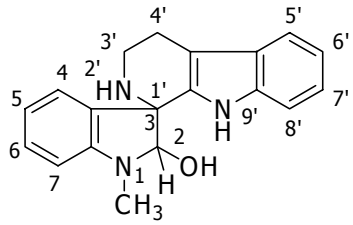
7.4.3 Partly reduced amide

Attempted preparation of spiro[(2,3-dihydro-2-hydroxy-1*H*-indole)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (269a)



A mixture of **250a** (69 mg, 0.24 mmol) and *Red-Al*® (*ca* 50%, 0.20 mL, 0.24 mmol) in dry toluene (4 mL) was stirred under a N_2 atmosphere at r.t. for 6 h. A solution of 5% NaOH (8 mL) was then added and toluene was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated to give only starting material (50 mg).

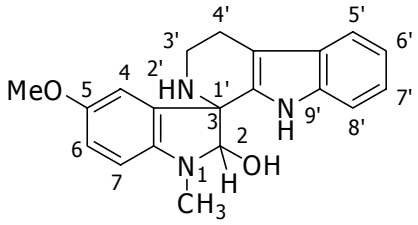
Preparation of spiro[(2,3-dihydro-2-hydroxy-1-methyl-1*H*-indole)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (269b)



A mixture of the spiro compound **250b** (0.15 g, 0.49 mmol) and *Red-Al*® (0.15 mL, 0.50 mmol) in dry toluene (4 mL) was stirred under a N_2 atmosphere at r.t. for 5 h (TLC showed no starting material was present after this

time). A solution of 5% NaOH (8 mL) was added and the toluene was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated to give an unstable oxyindoline, whose colour changed on a silica column and a PTLC, and in $CDCl_3$ (0.13 g). It was thus used without further purification. ^{1}H NMR ($CDCl_3$) δ 2.86 (m, 2H, CH_2-4′), 2.92 (s, 3H, CH_3), 3.13 (m, 1H, C*H*H-3′), 3.40 (m, 1H, CH*H*-3′), 4.96 (s, 1H, CH), 6.60 (d, *J*= 8.1 Hz, 1H, H-7), 6.69 (d, *J*= 7.2 Hz, 1H, H-5), 6.98 (d, *J*= 7.2 Hz, 1H, H-4), 7.10-7.23 (m, 4H, Ar), 7.51 (dd, *J*= 6.9, 1.5 Hz, 1H, H-5′), 7.72 (br s, 1H, NH); EI-MS *m/z* 305 ($[M]^+$, 60%).

Preparation of spiro[(2,3-dihydro-2-hydroxy-5-methoxy-1-methyl-1*H*-indole)-3,1′-(1′,2′,3′,4′-tetrahydro-9*H*-pyrido[3,4-*b*]indole)] (269c)

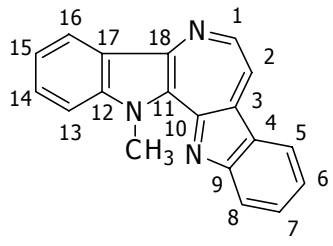


A mixture of the spiro compound **250c** (0.16 g, 0.49 mmol) and *Red-Al*® (0.15 mL, 0.50 mmol) in dry toluene (4 mL) was stirred under a N_2 atmosphere at r.t. for 5 h (TLC showed no starting material was present after this time). A solution of 5% NaOH (8 mL) was added and the toluene was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated to give an unstable oxyindoline, whose colour changed on a silica column and on PTLC, and in $CDCl_3$ (85 mg). It was thus used without further purification. ^{1}H NMR ($CDCl_3$) δ 2.86 (m, 2H, CH_2-4′), 2.89 (s, 3H, CH_3), 3.08 (m, 1H, C*H*H-3′), 3.37 (m, 1H, CH*H*-3′), 3.61 (s, 3H, OCH_3), 4.88 (s, 1H, CH), 6.54 (d, *J*= 8.4 Hz, 1H, H-7), 6.59 (d, *J*= 2.7 Hz, 1H, H-4), 6.80 (dd, *J*= 8.7, 2.7 Hz, 1H, H-6), 7.10-7.19 (m, 2H, H-6′ and H-7′), 7.22 (d, *J*= 6.9 Hz, 1H, H-8′), 7.53 (d, *J*= 7.2 Hz, 1H, H-5′), 7.73 (br s, 1H, NH).

7.4.4 Rearrangement

Preparation of the azepino bisindole and its trifluoroacetate salt (270)

Note: The numbering used for **270** in the figure is the same as that used for iheyamine A and is not systematic.



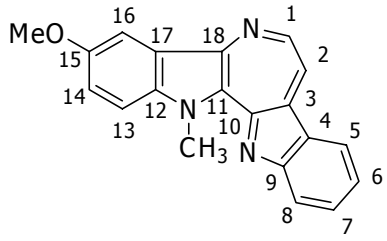
The hydroxyindoline **269b** (0.13 g) in 5M HCl (20 mL) was warmed to 90 ^{o}C for 30 min and then basified with 25% KOH until the pH was >12. The black precipitate formed was filtered through a sintered glass funnel. The solid was subjected to flash column chromatography (silica gel, 1% DCM/MeOH) to give the title compound **270** (21 mg, 17% over 2 steps from **250b**) as a green solid; mp 193-195 ^{o}C; UV (EtOH): λ_{max}= 236 (ε 115,022), 249 (ε 105,022), 308 (ε 157,152), 328 (ε 173,497), 445 (ε 37,085) nm; ^{1}H NMR ($CDCl_3$) δ 4.14 (s, 3H, CH_3), 7.41 (td, *J*= 8.1, 1.2 Hz, 1H, H-6), 7.61 (m with dd prominent, *J*= 8.7, 1.2 Hz, 2H, H-14 and H-15), 7.72 (dd, *J*= 6.9, 1.2 Hz, 1H, H-13), 7.80 (td, *J*= 8.1, 1.2 Hz, 1H, H-7), 8.13 (d, *J*= 8.1 Hz, 1H, H-5), 8.27 (d, *J*= 7.8 Hz, 1H, H-8), 8.39 (d, *J*= 5.7 Hz, 1H, H-2), 8.97 (d, *J*= 6.3 Hz, 1H, H-1), 9.60 (d, *J*= 8.1 Hz, 1H, H-16); ^{13}C NMR ($CDCl_3$) δ 28.7 (CH_3), 109.4 (C-15), 112.2 (C-18), 119.2 (C-5), 120.1 (C-2), 121.6 (C-6), 121.7 (C-8), 122.3 (C-14), 125.8 (C-3), 127.2 (C-16), 128.7 (C-13), 130.2 (C-17), 132.6 (C-7), 139.8 (C-11), 145.5 (C-1), 147.0 (C-4), 147.4 (C-12), 158.0 (C-10), 160.0 (C-9); EI-MS *m/z* 283 ($[M]^+$, 100%); HRCI-MS *m/z* calcd for ($[M+H]^+$ $C_{19}H_{14}N_3$: 284.1188, found: 284.1178.

The trifluoroacetate salt of **270** was prepared by reaction of **270** (20 mg, 0.071 mmol) with trifluoroacetic acid (8 μL, 0.11 mmol) in DCM (3 mL). After stirring at r.t. for 3 h, DCM and excess trifluoroacetic acid was evaporated to dryness and the residue was analysed by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, isomer ratio 2:1*) δ 3.93* (s, 1H,

CH_3), 4.01 (s, 2H, CH_3), 6.86-7.02 (m, 4.5H, Ar), 7.20* (d, *J*= 7.8 Hz, 0.5H, Ar), 7.30-7.37 (m, 3H, Ar), 7.46 (t, *J*= 7.8 Hz, 1H, Ar), 7.55 (d, *J*= 8.0 Hz, 1H, Ar), 7.58-7.65 (m, 1.5 H, Ar), 7.93 (d, *J*= 8.1 Hz, 1H, Ar), 8.00* (d, *J*= 8.1 Hz, 0.5 H, Ar), 8.08* (d, *J*= 7.8 Hz, 0.5H, Ar), 8.21 (d, *J*= 5.7 Hz, 1H, H-2), 8.62 (d, *J*= 7.5 Hz, 1H, Ar), 8.94 (d, *J*= 5.4 Hz, 1H, H-1), 9.30 (d, *J*= 8.1 Hz, 1H, Ar), 10.28* (s, 0.5H, NH), 11.40* (s, 0.5H, NH).

Preparation of the azepino bisindole (271)

Note: The numbering used for **271** in the figure is the same as that used for iheyamine A and is not systematic.



The hydroxyindoline **269c** (85 mg) in 5M HCl (15 mL) was warmed to 90 ^{o}C for 30 min and then basified with 25% KOH until the pH was >12. The black precipitate formed was filtered through a sintered glass funnel. The solid was subjected to flash column chromatography (silica gel, 1% DCM/MeOH) to give the title compound **271** (8 mg, 10% over 2 steps from **269c**) as a purple solid, mp 147-148 ^{o}C; UV (EtOH): λ_{max}= 250 (ε 16,475), 338 (ε 39,642), 370 (sh; ε 15,000), 490 (ε 7,667) nm; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H, CH_3), 5.00 (s, 3H, OCH_3), 7.37 (dd, *J*= 8.7, 2.4 Hz, 1H, H-14), 7.52 (br dd, *J*= 7.5, 6.6 Hz, 1H, H-6), 7.58 (d, *J*= 8.7 Hz, 1H, H-13), 7.80 (br dd, *J*= 8.1, 7.5 Hz, 1H, H-7), 7.98 (d, *J*= 2.4 Hz, 1H, H-16), 8.14 (d, *J*= 8.4 Hz, 1H, H-8), 8.35 (d, *J*= 7.5 Hz, 1H, H-5), 8.50 (d, *J*= 6.0 Hz, 1H, H-2), 8.96 (d, *J*= 5.4 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 30.0 (CH_3), 56.3 (OCH_3), 102.4 (C-16), 111.4 (C-14), 119.5 (C-5), 120.2 (C-2), 121.1 (C-6), 122.1 (C-8), 122.8 (C-13), 126.8 (C-4), 127.2 (C-17), 129.0 (C-3), 131.0 (C-10), 131.1 (C-12), 131.2 (C-7), 136.6 (C-18), 140.6 (C-1), 143.1 (C-9), 151.0 (C-11), 156.5 (C-15); EI-MS *m/z* 313 ($[M]^+$, 51%); HREI-MS *m/z* calcd for ($[M]^+$ $C_{20}H_{15}N_3O$: 313.1215, found: 313.1210

7.4.5 *N*-demethylation

Attempted *N*-demethylation of 270 using 2,2,2-trichloroethylchloroformate

A mixture of compound **270** (21 mg, 0.074 mmol), 2,2,2-trichloroethyl chloroformate (11 μL, 0.084 mmol) and anhydrous K_2CO_3 (10.2 mg, 0.074 mmol) in dry benzene (5 mL) under an Ar atmosphere was heated at reflux for 4 days. Methanol (15 mL) was then added and the reaction mixture was evaporated to dryness. The residue was dissolved in DCM (10 mL) and washed with water (3 x 10 mL). The organic extract was separated, dried and concentrated. The ^{1}H NMR spectroscopic analysis of the residue showed only starting material was obtained.

Attempted *N*-demethylation of 271 using thiophenol and $BF_3.Et_2O$

A mixture of compound **271** (21 mg, 0.067 mmol) and $BF_3.Et_2O$ (12 μL, 0.10 mmol) in dry THF (3 mL) was stirred under a N_2 atmosphere for 10 min. An excess of thiophenol (0.5 mL) in dry THF (3 mL) was then added and the reaction mixture was heated at reflux for 3 days. Satd. aqueous $KMnO_4$ solution (30 mL) and DCM (25 mL) were added to the reaction mixture. The organic extract was separated, washed sequentially with water (20 mL) and brine (20 mL), then dried and concentrated. The residue was subjected to PTLC (silica gel, DCM) to give three major product bands, which could not be identified. However, no starting material **271** or demethylated product, iheyamine A, was observed on the basis of ^{1}H NMR and MS analysis.

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Appendix

1.1 Antibacterial testing methodology[206]

The Mueller-Hinton Broth (MHB) Medium culture media was prepared with final concentration of 1 μg/mL $MgCl_2$ and 2 μg/mL $CaCl_2$ and was pre-warmed for 2-3 hours at 37 °C before use. Mueller-Hinton Agar (MHA) Medium culture media was prepared with final concentration of 1.5% Agar (Meck Agar 1.01614). *S. aureus* was streaked onto MHA and the plate was incubated overnight at 37 °C. From this plate, 10 cryovial were prepared by looping several colonies into 0.5 mL of 20% glycerol solution and were immediately stored at -140 °C. A cryovial was removed from -140 °C storage and thawed at room temperature. The MHA plate was streaked with a loopful of bacterial suspension and incubated overnight at 37 °C to create a parent plate (P1). The P1 was stored at -4 °C. A daughter plate (D1) was incubated overnight at 37 °C and its loop of colony was used to inoculate at 125 mL flask containing 20 mL of MHB, 25 μg/mL $CaCl_2.2H_2O$ and 12.5 μg/mL $MgCl_2.6H_2O$. The flask was shaken at 260 round/minute (rpm) for 18 hours at 37 °C on an orbital incubator shaker. The parent plates 1 and 2 were each used twice to generate two daughter plates (D1 and D2) before being discarded.

The standardized inocula for assays were prepared as 1/10 dilution of seed cultures by adding 250 μL of the cultures to 2,250 μL of MHB in a disposable cuvette and the required dilution factor was calculated by diving the observed OD_{650}. Sufficient volumes of the final inoculum cultures were prepared in pre-warmed MHB (37 °C) by diluting the standardized cultures to the required final concentration (10^8 dilution).

1.2 Assay procedure for 96-well microtitre plates

To each well of the 96-well microtitre plate was added 50 μL of liquid medium and 50 μL of peptoid test solution which was prepared by dissolving in 2.5% DMSO was added in triplicate to the top of the microtitre plate. A vancomycin control set (triplicate) and a compound negative control set (triplicate) were also set up on each plate. The inoculated culture medium was incubated at 37 °C for 30 minute shaking at 130 rpm and using the multichannel pipette and multistepper pipette, the adding, transferring and mixing of the inoculum were performed in the wells of the plates. The plates were incubated at 37 °C for 18 hours shaking at 100 rpm in an environment with 90% relative humidity and the results were recorded as the highest dilution of test compound that prevented bacterial growth (MIC). The MIC was also determined for DMSO (2.5%) as a control measure.

1.3 Antimalarial assay method

Samples were made up in DMSO solution. Using the Microdilution Radioisotope Technique, the sample (25 μL, in the culture medium) was placed in triplicate in a 96-well plate. Red blood cells (200 μL) infected with *Plasmodium falciparum* with a cell suspension (1.5%) of parasitemia (0.5-1%) were added to the wells. The range of the final concentrations of the samples varied from 1×10^{-5} to 1×10^{-8} g/mL with 0.1% of the organic solvent. The plates were cultured under standard conditions for 24 hours and the ^{3}H-hyphoxanthine (25 μL, 0.5 mCi) was added. The culture was incubated for 18-20 hours. The parasite's DNA was then harvested from the culture onto glass fibre filters. A radiation counter determined the amount of ^{3}H-hyphoxanthine. The inhibitory concentration of the sample was determined from its dose-response curves or by calculation.

The Trager and Jensen method[207] was used to culture *Plasmodium falciparum* K1 strain. The parasites were maintained in human red blood cells in a culture medium. RPM1 1640 was supplemented with 25 mM HEPES, 0.2% sodium bicarbonate, and 8% human serum, at 37 °C in a CO_2 incubator.